Research Article

Heart rate variability in nondiabetic dyslipidemic young Saudi adult offspring of type 2 diabetic patients

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Abstract

Background: Autonomic imbalance has been described in first-degree relatives of diabetic patients, and dyslipidemia has been reported to induce sympathovagal imbalance (SVI). **Aims and Objective:** To assess the contribution of dyslipidemia to SVI in adults with positive family history of type 2 diabetes mellitus (T2DM). **Materials and Methods:** This is a cross-sectional study involving 150 male Saudi adults aged 19–30 years, recruited from students of College of Applied Medical Sciences in Taif University, Taif, Saudi Arabia. Lipid profile, atherogenic index (AI), body mass index (BMI), waist circumference (WC), basal heart rate (BHR), blood pressure (BP), spectral indices of heart rate variability (HRV), and homeostatic model of insulin resistance (HOMA-IR) were measured and analyzed in study groups (control subjects with no family history of T2DM, $n = 50$; positive family history of T2DM, nondyslipidemic subjects, $n = 50$ and dyslipidemic subjects $n = 50$). **Result:** In the dyslipidemic group, lipid profile, LF-HF (ratio of low-frequency to high-frequency power of HRV, a precise indicator of SVI) was significantly increased ($P < 0.05$) when compared with non dyslipidemic and the control groups. Increased SVI was owing to simultaneous sympathetic motivation and vagal inhibition. LF-HF ratio was positively correlated with the WC, SBP, DBP, BHR, total cholesterol (TC), low-density lipoprotein (LDL) and AI. Significant contribution of WC, DBP, BHR, TC, and AI to the LF-HF ratio in the dyslipidemic group was observed by multiple regression analysis. **Conclusion:** SVI in dyslipidemic subjects with family history of T2DM occurs owing to sympathetic activation and vagal depression. Dyslipidemia contributes to the SVI in these subjects.

KEY WORDS: Dyslipidemia; positive family history of T2DM; Saudi

Introduction

Heart rate variability (HRV) has achieved an importance in recent years as a noninvasive technique that has been engaged in various fields of health and disease via its time- and frequency-domain analysis and employed to explore the autonomic nervous system (ANS).[1,2]

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The HRV refers to minute fluctuations between normal sinus heartbeats which are often represented by the consecutive RR intervals from the ECG data. Former outcomes have already linked the HRV alterations to cardiovascular diseases (CVDs).[3–5] The beat-to-beat fluctuation of heart rate reflects the cardiac ANS control[6] and helps in diagnosis of early pathophysiological conditions before symptoms grow to be manifesting.[7] HRV testing is a clinically relevant measure and provides key information about autonomic—parasympathetic and sympathetic—modulation of the cardiovascular system.[8] Diabetes can lead to dysfunction in the ANS causing various cardiovascular disorders. Because neuropathy first affects the longest nerve fibers, the first sign of diabetic

cardiac autonomic neuropathy tends to be linked to vagus nerve damage, which is responsible for nearly 75% of parasympathetic activity.[9,10]

Individuals with type 2 diabetes mellitus (T2DM) are recognized to be at an increased risk for early onset of CVD, which is a well-known macrovascular complication of T2DM. The death rate from CVD in adults with any type of diabetes is 1.7 times higher than in nondiabetic adults.[11] CVD risk factors have been shown to differ by ethnicity.[12] One of these risk factors is the positive family history of T2DM.[13] Taking into account the interplay of genetic background and epigenetic and lifestyle influences, it is suitable that the correlation between family history of diabetes and the risk for CVD in offspring may differ for persons of varying racial or ethnic backgrounds.[14] A positive family history of type 2 diabetes (FHD) nearly doubles the risk of diabetes in the offspring.[15] Because FHD is associated with all characteristic features of diabetes, such as high fasting plasma levels of glucose, lipids, systolic blood pressure (SBP), and body mass index (BMI).[16] To the best of our knowledge, little is known about the cardiac autonomic performance of the male offspring of T2DM subjects in the Saudi population. So, the aim of this study was to investigate the influence of positive FHD with or without dyslipidemia on cardiac autonomic function by examining the HRV in a group of young adult male in Saudi offspring of T2DM patients.

Materials and Methods

Study Design and Setting

A cross-sectional study was guided from March to September 2015, involving healthy 150 male students at College of Applied Medical Sciences in Taif University, Taif, Saudi Arabia. All individuals included in this study were subjected to full history taking, focusing on FHD, hypertension, smoking, and physical activity. Thorough clinical examination was done for all participants who gave an informed consent after attaining the approval of Research and Ethics Committee of Taif University.

Sample Size

A total of 264 students were studying in different levels in this faculty during the study period. Total coverage was approved, and all students were asked to participate in the study. The purpose of the study was clarified to the students, and verbal and written consents were taken. The response rate was 56.81%, and a total of 150 students comprised the subjects of the study. Participants were allowed to fill the questionnaire, and only 150 of them were eligible for the study.

Study Population

To be suitable for this study, subjects were chosen among healthy, physically fit, and those aged from 19 to 30 years. Fit participants were interviewed and clarified about their participation and the nature of investigations to be conducted in the study. Before the recordings, informed written consent was obtained from all of them.

Grouping

Group I: Control group with negative FHD: Fifty young, healthy, nondiabetic, nonobese, nondyslipidemic volunteers were selected as control subjects for this study.

Group II: Nondiabetic, nonobese, nondyslipidemic group with positive FHD: This group included 50 nondiabetic, nonobese, nondyslipidemic subjects.

Group III: Non-diabetic, nonobese, dyslipidemic group with positive FHD: This group included 50 nondiabetic, nonobese, dyslipidemic subjects.

Eligible Criteria

The criteria for nondiabetic, nonobese, dyslipidemic subjects were based on the National Cholesterol Education Program Adult Treatment Panel III (2002) (NCEP ATP III) guidelines.[17]

- Abdominal obesity was defined as waist circumference (WC) exceeding 102 cm in men.
- Fasting serum triglycerides (TGs) more than 150 mg/dL(1.7 mmol/L).
- Fasting serum high-density lipoprotein cholesterol (HDL-C) less than 40 mg/dL (1.0 mmol/L) in men.
- Fasting blood sugar (FBS) $<$110 mg/dL (6.1 mmol/L).

Subjects were chosen among male subjects with age ranging from 19–30 years

Exclusion Criteria

A medical history of any diseases known to affect the autonomic cardiac function such cardiovascular dysfunctions, neurological diseases, endocrine disorders, and taking medication were excluded from the study.

Anthropometric and Blood Pressure Measurements

Body weight and height were measured in subjects clothed in a light gown without shoes; these measurements were used to calculate the BMI (kg/m^2). WC and blood pressure (BP) measurements were done for the subjects in all the groups. BP measurements were performed with a standard manual sphygmomanometer, while the participants were in sitting position. Mean arterial pressure (MAP) was calculated.

Sampling

A total of 5 mL each of antecubital venous blood sample was collected after 12–14 h fasting under complete aseptic precautions in plain test tubes without anticoagulant. After coagulation, samples were centrifuged (at 1,500 $\times$ g for 15 min). The separated serum was divided into three aliquots. One was selected for the immediate assay of fasting glucose and lipid profile. The other two aliquots were stored at -20°C for subsequent assay of insulin. Repeated freezing and thawing were avoided. Hemolyzed samples were discarded.

Analytical Methods

Lipid profile concentrations (TG, TC: total cholesterol, and HDL: high-density lipoprotein) were determined using (Hospitex Diagnostics kits, Italy) and Hospitex Diagnostics (Eos Bravo Forte Ref.: LICG902 -automated chemistry analyzer, Italy), in accordance with the manufacturer's protocol. Low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were calculated by Friedewald equation: LDL = TC- (HDL + VLDL), VLDL = TG/5. Glucose was measured in 12 μL sera with the glucose oxidase method using the same automated chemistry analyzer. The ELISA for insulin (RAB0327; Sigma-Aldrich) was performed using ELISA reader (Bio Tek ELx800, USA).[18] Homeostatic Model Assessment-Insulin Resistance Index (HOMA-IR) was calculated using the equation: HOMA-IR = Fasting glucose (mg/dL) × fasting insulin (μU/mL)/405. The cutoff point to define insulin resistance was HOMA-IR $\geqslant$ 3.8.[19] The atherogenic index (AI) calculated as $\log_{10}$ (TG/HDL) has been reported as an significant predictor of atherosclerosis.[20]

Heart Rate Variability

All subjects fasted and finished their health checkup before the assessment of their HRV. Routine electrocardiogram (ECG) was performed between 9 and 11 am in the Physiology Laboratory, College of Applied Medical Sciences Taif, Kingdom of Saudi Arabia, under standardized conditions.[21,22] Fifteen minutes resting Lead II ECG was obtained (AD Instruments). An artifact-free 5-min segment of the ECG was analyzed offline using LabChart software that permits visual inspection of the raw ECG, so as to obtain the HRV parameters in time domain and frequency domain. The recorded ECG signals were conveyed through analog digital converter FE132 Bio Amp (using Power Lab, 8/35 model PL3508 8 channel data acquisition system, AD Instruments, Australia) with a sampling rate of 20 Hz.

Time-Domain Analysis

This involves comparing two different signals, and data were analyzed using descriptive statistical measures. The heart rate fluctuations were measured using various variables including,

(a) Standard deviation of RR intervals sensitive to all sources of variation (SDNN).

(b) Standard deviation of the averages of NN intervals in all 5 min-segments of the entire recording (SDANN).

(c) Root mean square successive difference of RR intervals (RMSSD).[21,22]

Frequency-Domain Analysis

The nonparametric Fast Fourier Technique (FFT) was performed for frequency-domain parameters. Different components of FFT with their specific frequency ranges include:

(a) Total power (TP) (0–0.4 Hz) which reflects sympathetic and parasympathetic tone.

(b) High frequency (HF) (0.15–0.4 Hz) which is indicative of parasympathetic tone and respiration.

(c) Low frequency (LF) (0.04–0.15 Hz) which indicates sympathetic and parasympathetic tone.

(d) Very low frequency (VLF) (0.003–0.04 Hz) which indicates thermoregulation and can be used to calculate LF normalized unit (LFnu) and HF normalized unit (HFnu) that represent the relative value of each component in proportion to the TP minus the VLF component.

(e) LF/HF which reflects sympathovagal balance and the sympathetic modulation.[21,22]

To limit the influence of diurnal and environmental variations, the HRV measurements were taken in the subjects in a sitting position after resting for 20 min. The measurements were taken in the morning and at the same room by one trained research assistant according to a standardized method. The HRV measurements were taken twice for each subject with a short-term interval in between. Premature beats (i.e. >20% shortening) were excluded manually and replaced with interpolated values and accounted for <1% of each participants' dataset. The same duration (5 min) of data were analyzed as established by the Task force system.[23] Recordings with nonsinus beats that were more than 1% of the total number of beats were also excluded. Premature beats and artifacts were carefully eliminated automatically and manually by visual inspection of all RR intervals.

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences software (SPSS version 22, SPSS Software Inc., Chicago, IL, USA). All the data were expressed as mean ± SD. Normality of data was tested by Kolmogorov–Smironov test. Statistical analysis of data within the three groups was done by one-way ANOVA and post hoc by Tukey–Kramer test. Pearson's correlation test was performed to determine the association between HRV indices and the study variables. The independent contribution of various factors such as age, BMI, SBP, and DBP to sympathovagal imbalance (LF-HF ratio) was assessed by multiple regression analysis. The *P* values less than 0.05 was considered statistically significant.

Result

Table 1 depicts the demographic and clinical parameters of the study groups. There were no statistically significant ($P > 0.05$) differences among the study groups regarding age, weight, height, WC, BMI, SBP, DBP, and BHR. Table 2 describes the glycemic status and lipid profile of the study groups. There were no statistically significant ($P > 0.05$) differences among the three groups regarding serum insulin, fasting blood glucose, and HOMA-IR. All lipid profile parameters (except HDL) and AI of plasma were significantly ($P < 0.05$) higher in the dyslipidemia group when compared with the nondyslipidemic group and the control group. Moreover, in the dyslipidemic group, HDL was significantly ($P < 0.05$) lower when compared with groups I and II. In the nondyslipidemic group, TC and LDL were significantly ($P < 0.05$) higher when compared with group I; however, HDL was significantly ($P < 0.05$) lower when compared with group I. Table 3 depicts the HRV indices among the study groups. Mean NN was significantly ($P < 0.05$) decreased in groups II and III

Table 1: Characteristics of the study groups according to the presence of family history of diabetes and dyslipidemia

Variable	Family history of DM			*P*
	Negative, group I, *n* = 50, control	Positive		
		Group II, *n* = 50, normolipidemic	Group III, *n* = 50, dyslipidemic	
Age (years)	22.2 ± 3.2	24.3 ± 6.4	23.5 ± 7.3	0.33
Weight (kg)	65.3 ± 21.6	67.3 ± 26.3[a]	66.5 ± 27.2[b]	0.92
Height (cm)	168.3 ± 15.9	170.4 ± 22.6	171.5 ± 19.4	0.40
WC (cm)	75.1 ± 11.4	73.8 ± 13.4[a]	74.2 ± 12.5[b]	0.87
BMI (kg/m^2)	24.81 ± 4.05	25.04 ± 4.28	24.92 ± 3.39	0.96
SBP (mm Hg)	116.47 ± 9.65	117.34 ± 3.44	119.25 ± 4.51	0.09
DBP (mm Hg)	65.79 ± 5.9	64.82 ± 6.3	66.50 ± 4.6	0.33
BHR (bpm)	83.4 ± 5.8	81.9 ± 6.2	84.7 ± 5.5	0.06

WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BHR, basal heart rate.
Data presented as mean ± SD; Group I: negative FHD normolipidemic subjects; Group II: positive FHD normolipidemic subjects; Group III: positive FHD dyslipidemic subjects.
[a]Comparison with group I; [b]Comparison with group II.
P is significant at 0.05.

when compared with the control subjects. The decrease was more prominent in group III. SDNN, SDDNN, and RMSSD were significantly ($P < 0.05$) decreased in the dyslipidemic group when compared with the nondyslipidemic and the control subjects. In addition, SDDNN and RMSSD were not significantly different from that in the control subjects. Among the frequency domain indices in the dyslipidemic group, TP, HF, VLF, and HFnu were significantly ($P < 0.05$) decreased. Moreover, LF, LFnu, and LF/HF ratio were significantly ($P < 0.05$) elevated when compared with the nondyslipidemic and the control subjects. In the nondyslipidemic group, TP and HF were significantly ($P < 0.05$) decreased; in the same time, LF/HF ratio and LF were significantly ($P < 0.05$) elevated when compared with the control subjects (group I). In Table 4, there was no significant correlation of any of the investigated parameters with LF/HF ratio in the nondyslipidemic and control groups. In study group, LF-HF ratio was positively correlated with the WC ($P = 0.047$) but not with BMI. LF-HF ratio was also correlated with SBP, DBP, BHR, TC, LDL, and AI; moreover, it was negatively correlated to HDL.

Multiple regression analysis demonstrated significant contribution of WC, DBP, BHR, TC, HDL, and AI to the LF-HF ratio in the dyslipidemic group [Table 5].

Discussion

In this study, there were no statistically significant differences among the study groups except for dyslipidemia. There are many articles that have described dyslipidemia in first-degree relatives (FDRs) of type 2 diabetic patients.[24,25] Many cardiovascular risk

Table 2: Comparison of biochemical parameters between the study groups

Variable	Family history of DM			*P*
	Negative, group I, *n* = 50, control	Positive		
		Group II, *n* = 50, normolipidemic	Group III, *n* = 50, dyslipidemic	
Insulin (uIU/mL)	10.6 ± 8.5	9.6 ± 7.6	11.4 ± 6.7	0.491
FBG (mg/dL)	76.3 ± 16.5	75.8 ± 19.4	78.6 ± 31.2	0.076
HOMA-IR	2.1 ± 1.5	2.3 ± 1.7	2.6 ± 1.9	0.342
TG (mg/dL)	120.2 ± 23.9	121.5 ± 29.6	159.6 ± 36.3[ab]	0.000*
TC(mg/dL)	152.4 ± 41.2	171.6 ± 39.2[a]	216.6 ± 57.4[ab]	0.000*
HDL (mg/dL)	46.8 ± 18.4	43.5 ± 21.7[a]	36.24 ± 9.6[ab]	0.000*
LDL (mg/dL)	95.4 ± 27.9	98.1 ± 26.3[a]	119.5 ± 37.6[ab]	0.000*
AIP	1.41 ± 2.4	1.50 ± 1.9	2.28 ± 3.1[ab]	0.000*

Data presented are mean ± SD; Group I: negative FHD normolipidemic subjects; Group II: positive FHD normolipidemic subjects; Group III: positive FHD dyslipidemic subjects; AIP: Atherogenic index of plasma.
[a]Comparison with group I; [b]Comparison with group II.
P is significant at 0.05.

Table 3: Frequency- and time-domain indices of HRV recorded in supine position of subjects in various groups

Variable	Family history of DM			*P*
	Negative, group I, *n* = 50, control	Positive		
		Group II, *n* = 50, normolipidemic	Group III, *n* = 50, dyslipidemic	
Time-domain analysis				
Mean NN	816.61 ± 56.99	672.42 ± 15.41[a]	591.05 ± 45.62[ab]	0.000
SDNN	86.77 ± 38.50	80.29 ± 4.38	37.26 ± 5.98[ab]	0.000
SDDNN	86.68 ± 48.86	85.54 ± 10.59	54.76 ± 4.67[ab]	0.000
RMSSD	91.09 ± 44.72	92.44 ± 33.89	42.64 ± 2.90[ab]	0.000
Frequency-domain analysis				
TP	8515.92 ± 743.15	1317.78 ± 230.14[a]	545.26 ± 108.71[ab]	0.000
LF	373.14 ± 108.07	1303.80 ± 281.42[a]	3859.25 ± 781.73[ab]	0.000
HF	452.86 ± 791.46	142.01 ± 41.32[a]	34.55 ± 15.74[ab]	0.000
LF-HF ratio	1.04 ± 0.32	2.23 ± 0.77[a]	3.38 ± 0.70[ab]	0.000
VLF	1014.29 ± 146.76	1131.92 ± 292.20	701.69 ± 103.99[ab]	0.000
LF nu	36.70 ± 10.84	37.94 ± 4.55	89.27 ± 3.81[ab]	0.000
HF nu	39.07 ± 6.78	38.02 ± 2.55	18.59 ± 3.37[ab]	0.000

Mean NN, mean NN interval; SDNN, standard deviation of normal to normal interval; SDANN, standard deviation of the averages of NN intervals in all 5-min segments of the entire recording; RMSSD, square root of the mean squared differences of successive normal to normal intervals. LF, low-frequency power; HF, high-frequency power; LF-HF ratio, ratio of low-frequency power to high-frequency power; HR, heart rate; TP, total power of HRV; VLF, very low-frequency power; LFnu, low-frequency power normalized; HFnu, high-frequency power normalized.
Data presented are mean ± SD; Group I: negative FHD normolipidemic subjects; Group II: positive FHD normolipidemic subjects; Group III: positive FHD dyslipidemic subjects.
[a]Comparison with group I; [b]Comparison with group II.
P values are probabilities for the difference between the subgroups in ANOVA. $P < 0.05$ is considered statistically significant.

factors can alter HRV. Among the studied risk factors are the different components of serum lipids. Dyslipidemia may be an important factor for the development of autonomic dysfunction, and data regarding correlations between serum lipids and HRV are controversial.[26] Some research has suggested that increased serum lipid fractions as low-density lipoprotein cholesterol (LDL-C) and TC were linked to a decreased HRV, although there are still some conflicting results.[27,28] So, we raised the question whether these conflicting results concerning the relationship between plasma lipid fractions and HRV could be applied to the nondiabetic dyslipidemic offspring of diabetic parents. In the dyslipidemia group, all lipid profile parameters (except HDL) and AI of plasma were significantly elevated. AI has lately been stated to be the better sign of CV risk.[29] However, HDL was significantly decreased. LF-HF ratio was positively correlated to TC, LDL, and AI. Moreover; it was negatively correlated to HDL. Multiple regression analysis demonstrated significant contribution of TC, HDL, and AI to the LF-HF ratio in the dyslipidemic group, while there was no significant correlation of any of the investigated parameters with LF-HF ratio in the nondyslipidemic and control groups signifying that atherogenic lipid risk factors contribute to SVI in dyslipidemic group. Our results are consistent with a recent study[30] which revealed that all lipid profile parameters except TG and VLDL and lipid risk factors (TC/HDL, TG/HDL, LDL/HDL, and AI) were significantly greater in FDRs men.

An increased LF-HF ratio, representing the SVI[31,32] was associated with increased LDL-C and TC levels, and these results are in accordance with previous studies regarding the general population.[33] A comparative study of plasma lipid profile in relation to HRV tests in healthy young population showed that TC and LDL-C levels were significantly increased in men. The same study showed that HDL-C levels were significantly decreased in men associated with decreased HRV compared with BMI and age-matched women.[34] So far, no correlation has been definitively established between serum TG values and HRV indices. Most studies have revealed that decreased HRV, as a strong predictor for CHD, was associated with hypercholesterolemia.[35,36] It may be observed that all these studies emphasize that the pathological lipid levels are associated with decreased HRV.

Our data support the hypothesis that dyslipidemia might cause disturbed ANS activity as evidenced by the significant decrease in all time-domain indices including, mean NN, SDNN, SDDNN, and RMSSD in the dyslipidemic group. In addition, the significant decrease in frequency-domain indices such as, TP, HF, VLF, and HFnu and the significant elevation in LF, LFnu, and LF-HF ratio in the dyslipidemic group were observed. Significant elevation in LF/HF ratio indicates greater SVI in dyslipidemic male subjects with positive FHD, which was contributed by both increased sympathetic (increased LF, LFnu) and decreased vagal (decreased HFnu and time-domain indices) tone.[37]

The TP of HRV was significantly decreased in dyslipidemic group; this represents a considerable decrease in HRV in these persons because TP represents the quantum of HRV spectrum and reflects overall vagal potency of cardiac modulation.[37]

Table 4: Correlation analysis of LF-HF ratio with studied parameters among all groups

	Group I, n=50, control		Group II, n=50, normolipidemic		Group III, n=50, dyslipidemic	
Parameters	***r***	***p***	**R**	***p***	***r***	***p***
WC	0.153	0.288	0.180	0.207	0.138*	0.047
BMI	0.249	0.081	0.075	0.624	0.087	0.214
SBP	0.071	0.623	-0.005	0.973	0.269**	0.000
DBP	0.157	0.277	0.273	0.055	0.425**	0.000
BHR	0.086	0.555	0.145	0.316	0.160*	0.021
HOMA-IR	0.181	0.209	0.069	0.302	0.062	0.371
TG	0.193	0.179	0.075	0.603	0.098	0.160
TC	0.086	0.555	-0.005	0.973	0.495**	0.000
HDL	-0.005	0.973	-0.132	0.361	-0.196**	0.005
LDL	0.263	0.065	0.078	0.202	0.251**	0.000
AI	0.266	0.062	0.071	0.623	0.876**	0.000

BMI, body mass index; WC, waist circumference; BHR, basal heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, Homeostatic model assessment of insulin resistance; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; AIP, atherogenic index of plasma.

Decrease in TP has been stated to be related to sudden cardiac death and cardiac morbidities.[38] Consequently, decreased TP of HRV in male FDRs of diabetic patients could predispose them to adverse CV events. Further, high BHR in these subjects increases their CV risk because increased resting heart rate has been reported as a CV risk.[30,39] SBP and DBP were significantly increased in dyslipidemic group. In addition, they were positively correlated to LF-HF ratio. Recently, prehypertension has been reported as a CV risk,[40] and SVI had a role of in the genesis of prehypertension.[41,42] Although WC was significantly correlated to LF-HF ratio, BMI had no independent BMI contribution to LF-HF ratio Thus, increased central adiposity appeared to be directly linked to SVI in these subjects. Thus, it appears that CV risks are more in male FDRs of type 2 diabetic patients, and SVI in these men is closely linked to these CV risks.[30]

The limitation of this study is that we have not estimated glycated hemoglobin. In addition, it includes a small number of patients who have fulfilled the inclusion criteria. Regarding the valuation of HRV indices, particularly frequency-domain indices, the guiding principles of the Task Force for Pacing and Electrophysiology[23] recommend optimal conditions as a temperature controlled and quiet room. In our study, these circumstances could not be exclusively satisfied.

Table 5: Multiple regression analysis of LF-HF ratio with studied parameters among dyslipidemic group

	Standardized beta	*P*
WC	0.567	0.000
DBP	1.681	0.000
BHR	0.951	0.027
TC	0.117	0.021
HDL	-0.469	0.000
AIP	0.815	0.000

WC, waist circumference; DBP, diastolic blood pressure; BHR, basal heart rate; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AIP, atherogenic index of plasma.

Conclusion

SVI in dyslipidemic subjects with FHD occurs owing to sympathetic activation and vagal depression. Dyslipidemia contributes to the SVI in these subjects.

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References

1. Sztajzel J. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Wkly. 2004;134(35–36):514–22.
2. Ji L, Li P, Li K, Wang X, Liu C. Analysis of short-term heart rate and diastolic period variability using a refined fuzzy entropy method. Biomed Eng Online. 2015;14:64.
3. Alici G, Ozkan B, Acar G, Sahin M, Yazicioglu MV, Bulut M, et al. Evaluation of autonomic functions by heart rate variability after stenting in patients with carotid artery stenosis. Ann Noninvasive Electrocardiol. 2013;18(2):126–9.
4. Rupprecht S, Hoyer D, Hagemann G, Witte OW, Schwab M. Central sleep apnea indicates autonomic dysfunction in asymptomatic carotid stenosis: a potential marker of cerebrovascular and cardiovascular risk. Sleep. 2010;33(3):327–3.
5. Hillebrand S, Gast KB, de Mutsert R, Swenne CA, Jukema JW, Middeldorp S, et al. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression. Europace. 2013;15 (5):742–9.
6. Kobayashi H. Inter- and intra-individual variations of heart rate variability in Japanese males. J Physiol Anthropol. 2007;26(2):173–7.
7. Liese AD, D'Agostino RB, Hamman RF, Kilgo PD, Lawrence JM, Liu LL, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics. 2006;118(4):1510–8.
8. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. J Diabetes Investig. 2013;4(1):4–18.
9. Faulkner MS, Hathaway DK, Milstead EJ, Burghen GA. Heart rate variability in adolescents and adults with type 1 diabetes. Nurs Res. 2001;50(2):95–104.
10. Balcıoğlu AS, Müderrisoğlu H. Diabetes and cardiac autonomic neuropathy: Clinical manifestations, cardiovascular consequences, diagnosis and treatment. World J Diabetes. 2015;6(1):80–91.
11. Centers for Disease Control and Prevention (2014). National Diabetes Statistics Report: Estimates of Diabetes and its Burden in

the United States, 2014. Atlanta, GA: US Department of Health and Human Services, 2014.
12. Forouhi NG, Sattar N. CVD risk factors and ethnicity—a homogeneous relationship? Atheroscler Suppl. 2006;7(1):11–9.
13. Szykowna I, Wasikowa R. [Evaluation of the risk of diabetes in the offspring of patients with diagnosis of type 2 diabetes]. Pediatr Endocrinol Diabetes Metab. 2009;15(2):71–83.
14. Law JR, Stafford JM, D'Agostino RB, Badaru A, Crume TL, Dabelea D, et al. Association of parental history of diabetes with cardiovascular disease risk factors in children with type 2 diabetes. J Diabetes Complications. 2015;29(4):534–9.
15. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med. 2007;167(10): 1068–74.
16. Wagner R, Thorand B, Osterhoff MA, Müller G, Böhm A, Meisinger C, et al. Diabetologia. 2013;56(10):2176–80.
17. National Institutes of Health. *Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).* National Institutes of Health. 2002. Downloaded from http://circ.ahajournals.org/ by guest on July 2, 2015.
18. Patel SJ, Hanks LJ, Ashraf AP, Gutierrez OM, Bamman MM, Casazza K. Effects of 8 week resistance training on lipid profile and insulin levels in overweight/obese peri-pubertal boys—a pilot study. J Diab Res Clin Metabol. 2015;4:2.
19. Ascaso JF, Romero P, Real JT, Priego A, Valdecabres C, Carmena R. [Insulin resistance quantification by fasting insulin plasma values and HOMA index in a non-diabetic population]. Med Clin (Barc). 2001;117(14):530–3.
20. Dobiasova M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma. (FER (HDL)). Clin Biochem. 2001;34(7):583–8.
21. Sathyaprabha TN, Satishchandra P, Netravathi K, Sinha S, Thennarasu K, Raju TR. Cardiac autonomic dysfunctions in chronic refractory epilepsy. Epilepsy Res. 2006;72(1):49–56.
22. Udupa K, Sathyaprabha TN, Thirthalli J, Kishore KR, Lavekar GS, Raju TR, et al. Alteration of cardiac autonomic functions in patients with major depression: a study using heart rate variability measures. J Affect Disord. 2007;100(1–3):137–41.
23. Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation. 1996;93:1043–65.
24. Altinli S, Elevli M, Ozkul AA, Kara PG, Karsidag K, Dogru M. Insulin resistance and metabolic syndrome in children of parents with diabetes mellitus. J Pediatr Endocrinol Metab. 2007;20(3):431–6.
25. Badea AR, Nedelcu L, Valeanu M, Zdrenghea D. The relationship between serum lipid fractions and heart rate variability in diabetic patients with statin therapy. Clujul Med. 2014;87(3):152–8.
26. Chaudhuri A, Borade NG, Hazra SK. A study of heart rate variability tests and lipid profile in postmenopausal women J Indian Medical Assoc. 2012;110(4):228:230–2.
27. Liu CC, Kuo TB, Yang CC. Effects of estrogen on gender-related autonomic differences in humans. Am J Physiol Heart Circ Physiol. 2003;285(5):H2188–2193.
28. Roy A, Kundu D, Mandal T, Bandyopadhyay U, Ghosh E, Ray D. A comparative study of heart rate variability tests and lipid profile in healthy young adult males and females. Niger J Clin Pract. 2013; 16(4):424–8.
29. Popa CD, Arts E, Fransen J, van Riel PL. Atherogenic index and high-density lipoprotein cholesterol as cardiovascular risk determinants in rheumatoid arthritis: the impact of therapy with biologicals. Mediators Inflamm. 2012;2012:785946.
30. Pal GK, Adithan C, Ananthanarayanan PH, Pal P, Nanda N, Durgadevi T, et al. Effects of gender on sympathovagal imbalance, prehypertension status, and cardiovascular risks in first-degree relatives of type 2 diabetics. Am J Hypertens. 2014;27(3): 317–24.
31. Amini M, Horri N, Zare M, Haghighi S, Hosseini SM, et al. People with impaired glucose tolerance and impaired fasting glucose are similarly susceptible to cardiovascular disease: a study in first-degree relatives of type 2 diabetic patients. Ann NutrMetab. 2010;56:267–272.
32. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010;141(2):122–31.
33. Lieb DC, Parson HK, Mamikunian G, Vinik AI. Cardiac autonomic imbalance in newly diagnosed and established diabetes is associated with markers of adipose tissue inflammation Exp Diabetes Res. 2012:878760.
34. Fu CH, Yang CC, Lin CL, Kuo TB. Alteration of cardiovascular autonomic functions by vegetarian diets in postmenopausal women is related to LDL cholesterol levels. Chin J Physiol. 2008;51(2):100–5.
35. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis Risk in Communities. Circulation. 2000;102(11):1239–44.
36. Doncheva NI, Nikolova RI, Danev SG. Overweight, dyslipoproteinemia, and heart rate variability measures. Folia Med (Plovdiv). 2003;45(1):8–12.
37. Malliani A. Heart rate variability: from bench to bedside. Eur J Intern Med. 2005;16(1):12–20.
38. Kiviniemi AM, Tulppo MP, Wichterle D, Hautala AJ, Tiinanen S, Seppanen T, et al. Novel spectral indexes of heart rate variability as predictors of sudden and non-sudden cardiac death after an acute myocardial infarction. Ann Med. 2007;39(1):54–62.
39. Jensen MT, Suadicani P, Hein HO, Gyntelberg F. Elevated resting heart rate, physical fitness and all-cause mortality: a 16-year follow-up in the Copenhagen Male Study. Heart. 2013;99(12):882–87.
40. Pal GK, Pal P, Nanda N, Amudharaj D, Adithan C. Cardiovascular dysfunctions and sympathovagal imbalance in hypertension and prehypertension: physiological perspectives. Future Cardiol. 2013;9(1):53–69.
41. Thiyagarajan R, Pal P, Pal GK, Subramanian SK, Bobby Z, Das AK, Trakroo M. Cardiovagal modulation, oxidative stress, and cardiovascular risk factors in prehypertensive subjects: cross-sectional study. Am J Hypertens. 2013;26(7):850–7.
42. Pal GK, Pal P, Nivedita N, Lalitha V, Dutta TK, Adithan C. Sympathovagal imbalance in young prehypertensives: importance of male-female difference. Am J Med Sci. 2013;345(1):10–7.

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