Decreased Baroreceptor Reflex Sensitivity in First-degree Relatives of Type 2 Diabetics is Linked to Sympathovagal Imbalance and Cardiovascular Risks

Gopal Krushna Pal[1]*, Pravati Pal[1], Nivedita Nanda[2], Venugopal Lalitha[1], Avupati Naga Syamsunder[1], Kuppusamy Saranya[1], Jagadeeswaran Indumathy[1], Allampalli Sirisha[1], Gopalakrishna Jayakrishnan[1]

[1]Department of Physiology, Jawaharlal Institute of Post-graduate Medical Education and Research, Puducherry, India, [2]Department of Biochemistry, JIPMER, Puducherry, India

ABSTRACT

Background: Though decreased baroreceptor reflex sensitivity (BRS) promotes cardiovascular (CV) morbidity and CV risks are reported in the first-degree relatives (FDR) of Type 2 diabetics, the pathophysiological mechanisms contributing to CV risks in these subjects are not yet elucidated. **Methods and Results:** Body mass index (BMI), CV parameters such as heart rate (HR), blood pressure (BP), rate-pressure product (RPP), stroke volume (SV), left-ventricular ejection time (LVET), cardiac output, total peripheral resistance (TPR) and BRS, spectral-indices of heart rate variability (HRV), autonomic function tests (AFT) and fasting blood glucose (FBG) were measured and analyzed in subjects of the study group (FDR of Type 2 diabetics, $n = 79$) and control group (subjects with no family history of diabetes, $n = 115$). BMI, HR, BP, RPP, SV, LVET, cardiac output, TPR, low-frequency to the high-frequency ratio (ratio of LF-HF power of HRV) and FBG were increased ($P < 0.0001$), and BRS was decreased ($P < 0.0001$) in the study group compared to the control group. AFT and HRV parameters demonstrated sympathovagal imbalance (SVI) in the study group, which was due to concomitant sympathetic activation and vagal inhibition. There was a significant correlation of BRS with BMI, CV parameters and LF-HF ratio, a sensitive marker of SVI. Multiple-regression analysis demonstrated independent contribution LF-HF ratio and hypertension status to BRS in the study group. Bivariate-logistic regression revealed significant prediction (odds ratio: 2.15; confidence interval: 1.1112-6.856, $P = 0.008$) of BRS to increased RPP, the marker of CV risk, in the study group. **Conclusion:** Decreased BRS in FDR of Type 2 diabetics predisposes them to CV dysfunction. BRS is linked to SVI and CV risks in these high-risk subjects.

Keywords: Autonomic derangement, baroreceptor reflex sensitivity, cardiovascular risk, first-degree relatives of Type 2 diabetics, heart rate variability, sympathovagal imbalance

INTRODUCTION

Recently, it has been reported that cardiovascular diseases (CVD) and diabetes mellitus are quite prevalent in younger age group in developing countries, especially in Indian sub-continent.[1,2] Diabetes and CVD share many common risk factors and the risk for mortality escalates with the co-occurrence of diabetes and CVD.[3] Hence, early detection and treatment of diabetes, especially at a younger age is among the major strategies to prevent the occurrence of CVD in the general population.[4] In general, the first-degree relatives (FDR) of diabetic patients are more prone to develop diabetes,[5] and the CV risks and prevalence of CVD are more in this high-risk population.[6,7] However, until date, no study has been conducted to elucidate the physiological mechanisms that predispose the FDR of Type 2 diabetics to increased CV risks.

Sympathovagal imbalance (SVI) has recently been reported to be associated with CV morbidities in different clinical

***Corresponding address:**
Dr. Gopal Krushna Pal, Professor and Head,
Department of Physiology, Jawaharlal Institute of Post-graduate Medical Education and Research, Puducherry - 605 006, India.
Phone: 0-91-93442 91160, Fax: 0-91-413-2272067,
E-mail: drgkpal@gmail.com

DOI: 10.5530/jcdr.2014.2.9

conditions.[8,9] SVI has also been proposed as the physiologic basis of metabolic derangements in diabetes mellitus.[10,11] An earlier study has reported autonomic imbalance with sympathetic hyperactivity in FDR of diabetic patients.[12] Though autonomic dysregulation has been reported in FDR of Type 2 diabetics,[12,13] the physiological basis of increased CV risks and contribution of autonomic imbalance to these risks in these subjects have not been studied. Recently, we have reported SVI in the form of sympathetic overactivity and vagal inhibition and the association of SVI with CV risks in FDR of Type 2 diabetics.[14] However, in this study, we had assessed CV risks without assessing CV dysfunctions.

Recently, spectral analysis of heart rate variability (HRV) has been documented as a tool for assessment of autonomic dysfunction in health and diseases.[15] Baroreceptor reflex sensitivity (BRS) assessed by continuous blood pressure variability (BPV) monitoring has long been established as a sensitive measure of SVI.[16] Furthermore, the BPV assessed by Finapres method records various CV parameters.[17-19]

Goals of this investigation

In the present study, we have assessed CV and autonomic functions in FDR of diabetic patients by HRV and BPV analysis, in addition to the assessment by conventional cardiac autonomic function tests (AFT). Furthermore, we have analyzed the association of BRS with SVI and CV risks in FDR of Type 2 diabetics.

MATERIALS AND METHODS

Study design and subjects

After obtaining the approval of Research Council and Institutional Ethics Committee, of Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, India, 194 subjects were recruited for this cross-sectional study from undergraduate medical and paramedical courses of JIPMER of 2013-2014 batches. They were classified into two groups.

1. Control group (n = 115): Normal healthy subjects without a family history of diabetes.
2. Study group (n = 79): Normal healthy FDR of patients with Type 2 diabetes mellitus. Subject of the study group (FDR of Type 2 diabetics) was defined as the subject having either of the parents or siblings diagnosed to have Type 2 diabetes mellitus for at least 1 year and receiving treatment for the same. This was done as part of a hypertension-diabetes research project, in which family history of diabetes was one of the questionnaires in the data sheet. The subjects were also interviewed, and hospital records examined to confirm the presence of diabetes in their family.

All subjects were examined clinically by a physician to rule out the presence of any acute or chronic illness. Healthy subjects (subjects without illness) were included in the study. Subjects receiving any medication, subjects with history of diabetes, smoking, hypertension, and hypertensive patients receiving medication were excluded from the study. As the level of physical fitness is a major determinant of sympathovagal tone,[20] subjects performing regular athletics and body building exercises were excluded from the study.

Recording of anthropometric and HRV parameters

Subjects were asked to report to AFT laboratory of physiology department at about 8 AM following overnight fast. The temperature of the laboratory was maintained at 25°C for all recordings. Their age, height, body weight, and body mass index (BMI) were recorded.

After 15 min of supine rest, electrocardiogram (ECG) was recorded for short-term HRV analysis following the procedures recommended by Task Force[21] using BIOPAC MP-100 data-acquisition system (BIOPAC Inc., Goleta, CA, USA). For the purpose, ECG electrodes were connected and lead II ECG was acquired at a rate of 1000 samples/s during supine rest using BIOPAC MP-100, continuously for 10 min. Data were transferred from BIOPAC to a windows-based personal computer (PC) with AcqKnowledge software version 3.8.2 (BIOPAC Inc., Goleta, CA, USA). Ectopics and artifacts were removed from the recorded ECG. The RR tachogram was extracted from the edited ECG using the R-wave detector in the AcqKnowledge software. HRV analysis was carried out using the HRV analysis software version 1.1 (Bio-signal Analysis group, Kuopio, Finland). Frequency-domain indices of HRV such as total power (TP), normalized low-frequency power (LFnu), normalized high-frequency power (HFnu), ratio of low-frequency to high-frequency power (LF-HF ratio), and time-domain indices such as the square root of the mean of the sum of the squares of the differences between adjacent NN intervals (root mean square successive difference [RMSSD]), standard deviation of normal to normal (SDNN) interval, number of interval differences of successive NN intervals >50 ms (NN50) and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50) were recorded.

Recording of CV parameters and BRS

The CV parameters and BRS were measured by continuous BPV method using Finapres (Finometer version 1.22a, Finapres Medical Systems, Amsterdam, The Netherlands); a non-invasive continuous hemodynamic CV monitor based on the principle of measurement of finger arterial pressure with the volume clamp technique of Penaz and the Physical criteria of Wesseling.[22] In this method, the brachial artery pressure measured was the reconstructed pressure from the finger pressure, estimated through generalized waveform inverse modeling and generalized level correction. The subjects were asked to lie down, and the brachial cuff of finapres was tied around the mid-arm about 2 cm above the cubital fossa and the finger cuff of small, medium or large size were tied around the middle phalanx of the middle finger depending on the finger width. For the height correction, two sensors were placed, one at the heart level and another at the finger level. The recordings were obtained following connection of cables of the cuffs to the Finometer, after ten minutes of supine rest. The "return to flow calibration and the physical" was done for the level correction between the brachial and finger pressure during the initial 5 min of the recordings. Following this, the continuous blood pressure (BP) recording was done for a period of 10 min.

The reconstructed brachial pressure was acquired through a PC based data acquisition system (Finapres Medical Systems BV, Amsterdam, The Netherlands). The parameters recorded from the reconstructed brachial pressure tachogram were heart rate (HR), systolic BP, diastolic BP, mean arterial pressure (MAP), rate-pressure product (RPP), interbeat interval, left ventricular ejection time (LVET), stroke volume (SV), cardiac output, total peripheral resistance (TPR), and BRS.

Recording of AFT parameters

Three conventional AFTs were performed following the standard procedures.[23]

HR and BP response to standing

The BP and ECG were recorded in the supine position. The subject was instructed to attain standing posture in 3 s. The ECG was continuously recorded during the procedure. The BP was recorded every 40 s by automatic BP monitor (Omron, SEM-1, Kyoto, Japan) until 5th min. The 30:15 ratio (ratio of maximum RR interval at 30th beat to minimum RR interval at 15th beat following standing) was calculated.

HR response to deep breathing

The subject in a sitting posture, HR, and respiration monitoring was done from ECG recording and stethographic respiratory tracings recorded on the multichannel polygraph (Nihon-Kohden, London, UK). A baseline recording of ECG and respiration was taken for 30 s. The subject was asked to take slow and deep inspiration followed by slow and deep expiration such that each breathing cycle lasted for 10 s, consisting of 6 breathing cycles/min. E: I ratio (ratio of average RR interval during expiration to average RR interval during inspiration in six cycles of deep breathing) was calculated from ECG tracing.

BP response to isometric handgrip

The baseline BP was recorded. The subject was asked to press handgrip dynamometer at 30% of maximum voluntary contraction for 2 min. The BP was recorded at 1st and 2nd min of contraction. ΔDBP_{IHG} (maximum rise in diastolic BP above baseline) was noted.

Estimation of fasting blood glucose (FBG)

FBG was estimated by glucose-oxidase method using glucometer (LifeScan Inc., Milpitas, CA, USA), following the finger prick technique.

Data analysis

SPSS version 13 (SPSS Software Inc., Chicago, IL, USA) and GraphPad InStat software (GraphPad Software Inc., San Diego, CA, USA) were used for statistical analysis. All data were expressed as mean ± SD. Normality of data was tested by Kolmogorov–Smirnov test. For parametric data, the level of significance between the groups was tested by Student's unpaired *t*-test and for non-parametric data Welch's corrected *t*-test was used. The association of BRS with BMI and CV parameters was assessed by Pearson's correlation analysis. The independent contribution of BMI, basal heart rate (BHR), LF-HF ratio, and prehypertension status to BRS was assessed by multiple regression analysis. Independent prediction of BRS to cardiac risk (increased RPP) was determined by bivariate logistic regression. The $P < 0.05$ was considered as statistically significant.

RESULTS

There was no significant difference in age ($P = 0.1178$) between the subjects of the control group and study group (Table 1). The BMI, HR, systolic BP (SBP), diastolic BP (DBP), MAP, RPP, SV, LVET, cardiac output and TPR of the study group subjects were significantly more ($P < 0.0001$) compared to that of the control group subjects

(Table 1). Interbeat interval and BRS were significantly decreased ($P < 0.0001$) in the study group. Among the frequency domain indices of HRV, TP, HF, and HFnu were significantly reduced ($P < 0.0001$) and LF, LFnu, and LF-HF ratio were significantly increased ($P < 0.0001$) in the study group subjects compared to the control group subjects. All the time domain indices (RMSSD, SDNN, NN50, and pNN50) were significantly less ($P < 0.0001$) in the study group subjects compared to that of the control group subjects. The E: I ratio was significantly decreased, and ΔDBP_{IHG} and 30:15 ratio were significantly increased ($P < 0.0001$) in the study group subjects (Table 1).

FBG was significantly high ($P < 0.0001$) in the study group subjects compared to that of the control group subjects (Table 1).

Though there was no significant correlation of BRS with any of the parameter in the control group, the correlation of BMI, CV parameters and LF-HF ratio with BRS was significant in the study group (Table 2).

Multiple regression analysis revealed significant individual contribution of BHR, LF-HF ratio and pulmonary prehypertension status, but not BMI to BRS in the study group (Table 3). Bivariate logistic regression (Table 4)

Table 1 Comparison of age, cardiovascular (CV), heart rate variability (HRV) and conventional autonomic function testing (CAFT) parameters of control group (subjects with no family history of diabetes) and study group (first degree relatives of type 2 diabetics) subjects

Parameters	Control group (*n*=115)	Study group (*n*=79)	*P* values
Age (years)	20.71±2.38	21.33±3.11	0.1178
Body mass index (kg/m^2)	23.12±3.48	25.95±3.56	<0.0001
CV parameters			
Heart rate (beats/min)	71.82±8.78	78.85±9.80	<0.0001
Systolic blood pressure (mmHg)	111.20±9.60	120.70±10.24	<0.0001
Diastolic blood pressure (mmHg)	70.08±6.12	81.80±7.37	<0.0001
Mean arterial pressure (mmHg)	83.65±6.40	94.63±3.88	<0.0001
Rate-pressure product (mmHg/min)	79.80±8.42	95.20±9.40	<0.0001
Stroke volume (ml)	68.80±7.23	74.78±9.56	<0.0001
Left ventricular ejection time (ms)	304.30±18.88	321.70±20.76	<0.0001
Cardiac output (L/min)	4.90±1.10	5.85±1.25	<0.0001
Interbeat interval (ms)	832.70±90.32	762.80±84.70	<0.0001
TPR (mmHg.min/l)	0.806±0.20	1.117±0.23	<0.0001
Baroreflex sensitivity (ms/mmHg)	26.70±8.76	19.10±7.96	<0.0001
HRV parameters			
Total power (ms^2)	955.86±266.20	650.76±215.70	<0.0001
Normalized LF (LFnu)	40.56±15.10	59.20±18.42	<0.0001
Normalized HF (HFnu)	59.15±16.28	40.56±15.38	<0.0001
LF:HF ratio	0.68±0.32	1.48±0.65	<0.0001
RMSSD (ms)	62.35±21.54	39.70±15.20	<0.0001
SDNN (ms)	47.30±17.26	31.32±12.48	<0.0001
NN50	54.70±20.67	30.53±11.28	<0.0001
pNN50	28.12±10.18	20.15±7.26	<0.0001
CAFT parameters			
E:I ratio	1.47±0.27	1.26±0.23	<0.0001
30:15 ratio	1.25±0.22	1.45±0.25	<0.0001
ΔDBP_{IHG}	20.32±5.38	27.20±6.24	<0.0001
Fasting blood glucose (mg%)	74.25±9.50	97.64±11.20	<0.0001

Data expressed as mean±SD. *P* value<0.05 was considered significant. TPR: Total peripheral resistance; LF-HF ratio: Ratio of low frequency to high frequency power; RMSSD: The square root of the mean of the sum of the squares of the differences between adjacent NN intervals; SDNN: Standard deviation of normal to normal interval; NN50: The number of interval differences of successive NN intervals greater than 50; 30:15 ratio: The ratio of maximum RR interval at 30th beat to minimum RR interval at 15th beat following standing; E:I ratio: The ratio of average RR interval during expiration to that of during inspiration in six cycles of deep breathing; ΔDBP_{IHG}: The maximum rise in DBP above baseline following 30% of maximum voluntary contraction by isometric handgrip method

Table 2 Correlation of BRS with various parameters in both the groups

Parameters	Control group (*n*=115)		Study group (*n*=79)	
	r	*P*	*r*	*P*
BMI	0.078	0.192	0.250	0.042
BHR	0.090	0.160	0.285	0.014
SBP	0.105	0.127	0.320	0.009
DBP	0.128	0.102	0.355	0.006
MAP	0.112	0.120	0.350	0.006
RPP	0.072	0.206	0.340	0.007
TPR	0.087	0.182	0.296	0.011
LF-HF ratio	0.152	0.084	0.412	0.001

The *P* value<0.05 was considered significant. BRS: Baroreceptor reflex sensitivity; BMI: Body mass index; BHR: Basal heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; RPP: Rate pressure product; TPR: Total peripheral resistance; LF-HF ratio: Low-frequency to high-frequency ratio of heart rate variability

Table 3 Multiple regression analysis of BRS (as dependable variable) with various parameters (as independent variables) in study group subjects

Independent variables	Standardized regression coefficient B	95% C.I.		*P* values
		Lower bound	Upper bound	
BMI	0.110	−0.215	0.506	0.142
BHR	0.205	0.027	0.178	0.033
LF-HF ratio	0.365	−0.045	0.155	0.005
PHTN status	0.517	0.004	0.009	<0.001

P values<0.05 considered significant. BRS: Baroreceptor reflex sensitivity; BMI: Body mass index; BHR: Basal heart rate; LF-HF ratio: Low-frequency to high-frequency ratio of heart rate variability; PHTN status: Prehypertension status

Table 4 Bivariate logistic regression analysis of BRS (as dependent variable) with RPP (as independent variable) in control group and study group subjects after adjusting for BMI

	Control group		Study group	
	OR (95% C.I.)	*P* value	OR (95% C.I.)	*P* value
RPP	0.84 (0.517 to 3.208)	1.256	2.15 (1.112 to 6.856)	0.008

P<0.05 considered significant; OR: Odds ratio; BRS: Baroreceptor reflex sensitivity; RPP: Rate pressure product; C.I.: Confidence interval

showed significant prediction of BRS to RPP in the study group (odds ratio [OR]: 2.15; confidence interval [CI]: 1.112-6.586; $P = 0.008$) compared to that of the control group (OR, 0.84; CI, 0.517-3.208; $P = 1.256$).

DISCUSSION

In the present study, BRS of the study group was significantly reduced (Table 1) indicating attenuation of CV health of FDR of Type 2 diabetics, as decreased BRS has been reported to be associated with CV morbidity.[24,25] Further, it has been recently reported that decrease in BRS can predict CV events in Type 2 diabetics.[26,27] Furthermore, it has been documented earlier that decrease in BRS predicts cardiac mortality in myocardial infarction patients.[28,29] Thus, decreased BRS in FDR of Type 2 diabetics as observed in the present study could increase their CV risks and predispose them to adverse CV events. The present study is the first of its kind assessing the status of BRS in FDR of Type 2 diabetics. The decrease in BRS was significantly correlated with RPP (Table 3) and had significant prediction of RPP (Table 4). RPP is a measure of myocardial workload and oxygen consumption, and increase in RPP is considered as a potential CV risk.[30] These findings indicate that decreased BRS is linked to increased RPP in FDR of Type 2 diabetics. Moreover, SBP, DBP, and MAP in the study group were significantly high compared to the control group (Table 1), further indicating poor CV health in FDR of Type 2 diabetics as high normal BP has been reported to increase the risk of CV diseases.[31,32] Moreover, BRS had independent prediction of prehypertension status in the study group subjects (Table 3).

TPR was significantly more in the study group subjects (Table 1). TPR, an indicator of sympathetic vasoconstrictor tone has been suggested as a predictor of CV disease risk in individuals who had more body size at birth.[33] Furthermore, TPR has been directly correlated with ventricular hypertrophy in hypertensives.[34] As an increase in TPR was significantly correlated with BRS in the study group subjects (Table 2), we presume the association of BRS to potential cardiac morbidities in these subjects. Moreover, SV and cardiac output were increased, and LVET was decreased in the study group, further highlighting the increased hemodynamic stress in FDR of Type 2 diabetics.

Arterial baroreceptors play a central role in BP regulation in response to various stimuli through alteration in both sympathetic and vagal activities, and therefore assessment of BRS provides the state of SVI in various CV disease states.[19] In the present study, BRS was significantly correlated with LF-HF ratio of HRV (Table 2). The LF-HF ratio was significantly increased in the study group (Table 1) indicating sympathetic accentuation and vagal inhibition in FDR of Type 2 diabetics as increase in LF-HF ratio represents facilitation of sympathetic drive and inhibition of vagal drive to the heart[15,21] LF-HF ratio is considered as a sensitive measure of SVI in various clinical disorders[8,9,15,21] Independent association of BRS with LF-HF ratio (Table 3) confirms the presence of SVI and contribution of SVI to CV risks in FDR of Type 2 diabetics. This corroborates with the findings of our recent report,[14] in which we did not assess cardiac parameters and BRS.

Findings of the present study demonstrate that the SVI in FDR of Type 2 diabetics is due to alterations in both sympathetic and parasympathetic activities. Increase in sympathetic activity was confirmed by higher LFnu in the study group subjects (Table 1), as increase in LFnu reflects increased cardiac sympathetic drive.[15,21] Inhibition of parasympathetic activity in these subjects was demonstrated by a decrease in HFnu, as decreased HFnu represents decreased vagal modulation of cardiac drive,[15,21] This was further confirmed by decreased time-domain indices of HRV in the study group, as time-domain indices represent parasympathetic modulation of cardiac activity.[15,21] Among HRV indices, RMSSD exclusively reflects vagal modulation of HR on a short-term basis and is considered as an important indicator of parasympathetic tone.[21] Significantly decreased RMSSD in the study group (Table 1) confirms poor cardiac vagal control in FDR of diabetic patients.

In addition, increase in ΔDBP_{IHG} in the study group subjects indicates increased sympathetic reactivity in response to isometric handgrip test in FDR of Type 2 diabetics, as ΔDBP_{IHG} reflects the state of sympathetic reactivity.[23] Increase in 30:15 ratio and decrease in E: I ratio represent decreased parasympathetic reactivity as these two ratios reflect modulation of vagal reactivity in response to orthostatic stress and deep breathing, respectively.[23] Thus, findings of the present study demonstrate SVI in FDR of Type 2 diabetics is due to increased sympathetic tone and reactivity and decreased vagal tone and reactivity.

The TP of HRV was significantly decreased in the study group subjects (Table 1) representing a substantial decrease in HRV in FDR of Type 2 diabetics as TP represents the quantum of HRV spectrum.[15,21] Recently, decrease in TP of HRV has been observed to be associated with sudden cardiac death and cardiac morbidities.[8,9,35,36] Thus, decreased HRV in FDR of diabetics patients makes them vulnerable to adverse CV events. Further, BHR was significantly high in these subjects (Table 1). Resting HR is an index of parasympathetic tone,[23] and increased BHR has been

reported to be associated with increased CV risks.[37] As BHR was significantly correlated with BRS (Table 2) and had independent association with BRS, the CV risks mediated through increased BHR in FDR of Type 2 diabetics are linked to the decrease in BRS.

Overweight is common in individuals with family history of diabetes.[38] In the present study, BMI was more in the study group compared to the control group (Table 1). Though BMI had significant correlation with BRS in the study group (Table 2), it had no independent association with BRS, demonstrated by multiple regression analysis (Table 3). Therefore, though BMI is associated with BRS in FDR of Type 2 diabetics, it does not appear to independently contribute to CV risks in these subjects.

FBG was significantly high in the study group subjects compared to that of control subjects (Table 1), indicating that the FDR of Type 2 diabetics are prone to develop diabetes. The limitation of the study is that we have not estimated the plasma insulin, and not assessed insulin resistance, dyslipidemia and oxidative stress that could contribute to SVI in FDR of Type 2 diabetics. Nevertheless, the results of the present study indicate the presence of SVI in the form decreased BRS and increased LF-HF ratio representing increased sympathetic and decreased parasympathetic activity in young FDR of Type 2 diabetics. The CV risk factors such as resting tachycardia, decreased TP of HRV, increased RPP, increased prehypertension status and decreased BRS were prominent in these subjects that were linked to decrease in baroreceptor sensitivity in FDR of Type 2 diabetics. Future studies should assess if restoration of sympathovagal homeostasis attained by non-pharmacological means such as yoga-relaxation would reduce the CV risks in the subjects, as practice of such techniques has been reported to restore sympathovagal balance.[39]

ACKNOWLEDGMENTS

The institute intramural fund of JIPMER was utilized for the conduct of this study. However, no external financial grant was used for this study.

REFERENCES

1. Pradeepa R, Prabhakaran D, Mohan V. Emerging economies and diabetes and cardiovascular disease. Diabetes Technol Ther 2012;14 Suppl 1:S59-67.
2. Joshi SR. Type 2 diabetes in Asian Indians. Clin Lab Med 2012;32:207-16.
3. Laslett LJ, Alagona P Jr, Clark BA 3rd, Drozda JP Jr, Saldivar F, Wilson SR, *et al*. The worldwide environment of cardiovascular disease: Prevalence, diagnosis, therapy, and policy issues: A report from the American College of Cardiology. J Am Coll Cardiol 2012;60:S1-49.
4. Anselmino M, Rydén L. Strategies to enhance cardiovascular disease prevention in patients with diabetes. Curr Opin Cardiol 2009;24:461-7.
5. Karaman A, Bayram F, Gundogan K, Ozsan M, Karaman H, Kelestimur F. Prevalence of diabetes mellitus and glucose metabolism disorders in the first degree relatives of type 2 diabetic patients. Bratisl Lek Listy 2012;113:361-7.
6. Johansen NB, Hansen AL, Jensen TM, Philipsen A, Rasmussen SS, Jørgensen ME, *et al*. Protocol for ADDITION-PRO: A longitudinal cohort study of the cardiovascular experience of individuals at high risk for diabetes recruited from Danish primary care. BMC Public Health 2012;12:1078.
7. Amini M, Horri N, Zare M, Haghighi S, Hosseini SM, Aminorroaya A, *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 Nutr Metab 2010;56:267-72.
8. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 2010;141:122-31.
9. Pal GK, Pal P, Nanda N, Amudharaj D, Adithan C. Cardiovascular dysfunctions and sympathovagal imbalance in hypertension and prehypertension: Physiological perspectives. Future Cardiol 2013;9:53-69.
10. Fleischer J. Diabetic autonomic imbalance and glycemic variability. J Diabetes Sci Technol 2012;6:1207-15.
11. 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;2012:878760.
12. Fiorentini A, Perciaccante A, Paris A, Serra P, Tubani L. Circadian rhythm of autonomic activity in non diabetic offsprings of type 2 diabetic patients. Cardiovasc Diabetol 2005;4:15.
13. Neves FJ, Bousquet-Santos K, Silva BM, Soares PP, Nóbrega AC. Preserved heart rate variability in first-degree relatives of subjects with type 2 diabetes mellitus without metabolic disorders. Diabet Med 2008;25:355-9.
14. Pal GK, Adithan C, Dutta TK, Pal P, Nanda N, Lalitha V, *et al*. Association of hypertension status and cardiovascular risks with sympathovagal imbalance in first degree relatives of type 2 diabetics. J Diabetes Investig 2013. (In Press).
15. Malliani A. Heart rate variability: from bench to bedside. Eur J Intern Med 2005;16:12-20.
16. Pellizzer AM, Kamen PW, Jackman G, Brazzale D, Krum H. Non-invasive assessment of baroreflex sensitivity and relation to measures of heart rate variability in man. Clin Exp Pharmacol Physiol 1996;23:621-4.
17. Jansen JR, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH. A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. Br J Anaesth 2001;87:212-22.
18. La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: measurement and clinical implications. Ann Noninvasive Electrocardiol 2008;13:191-207.
19. Rovere MT, Maestri R, Pinna GD. Baroreflex sensitivity assessment: latest advances and strategies. Eur Cardiol 2011;7:89-92.
20. Jensen-Urstad K, Saltin B, Ericson M, Storck N, Jensen-Urstad M. Pronounced resting bradycardia in male elite runners is associated with high heart rate variability. Scand J Med Sci Sports 1997;7:274-8.
21. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043-65.
22. Imholz BP, Wieling W, van Montfrans GA, Wesseling KH. Fifteen years experience with finger arterial pressure monitoring: Assessment of the technology. Cardiovasc Res 1998;38:605-16.
23. Low PA. Laboratory evaluation of autonomic function. Suppl Clin Neurophysiol 2004;57:358-68.
24. van Lill L, Malan L, van Rooyen J, Steyn F, Reimann M, Ziemssen T. Baroreceptor sensitivity, cardiovascular responses and ECG left ventricular hypertrophy in men: the SABPA study. Blood Press 2011;20:355-61.
25. Svacinová J, Moudr J, Honzíková N. Baroreflex sensitivity: diagnostic importance, methods of determination and a model of baroreflex blood-pressure regulation. Cesk Fysiol 2013;62:10-8.
26. Yufu K, Takahashi N, Okada N, Wakisaka O, Shinohara T, Nakagawa M, *et al*. Gender difference in baroreflex sensitivity to predict cardiac and cerebrovascular events in type 2 diabetic patients. Circ J 2011;75:1418-23.

27. Murozono Y, Yufu K, Takahashi N, Okada N, Shinohara T, Nakagawa M, *et al.* Combined assessment of baroreflex sensitivity with iodine 123 metaiodobenzylguanidine scintigraphic findings strengthens the power of predictive value for cerebral and cardiovascular events in type 2 diabetic patients. Circ J 2013;77:130-6.
28. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998;351:478-84.
29. La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. Circulation 1988;78:816-24.
30. White WB. Heart rate and the rate-pressure product as determinants of cardiovascular risk in patients with hypertension. Am J Hypertens 1999;12:50S-5.
31. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, *et al.* Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001;345:1291-7.
32. Lewandowski J, Artyszuk L, Ostrowski F, Ciszewski J, Puchalska L, Abramczyk P. Individuals with high-normal blood pressure have different metabolic and haemodynamic characteristics to those with optimal blood pressure. Kardiol Pol 2012;70:252-8.
33. Feldt K, Räikkönen K, Pyhälä R, Jones A, Phillips DI, Eriksson JG, *et al.* Body size at birth and cardiovascular response to and recovery from mental stress in children. J Hum Hypertens 2011;25:231-40.
34. Chen HI. Hemodynamic mechanism of ventricular hypertrophy in hypertension. Chin J Physiol 2012;55:369-79.
35. Kiviniemi AM, Tulppo MP, Wichterle D, Hautala AJ, Tiinanen S, Seppänen 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;39:54-62.
36. Laitio T, Jalonen J, Kuusela T, Scheinin H. The role of heart rate variability in risk stratification for adverse postoperative cardiac events. Anesth Analg 2007;105:1548-60.
37. 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;99:882-7.
38. Soltanian N, Amini A, Iraj B, Askari G, Ebneyamin S, Ghias M, *et al.* Weight status of the first-degree relatives of patients with type 2 diabetes based on the glucose tolerance test. J Res Med Sci 2012;17:269-74.
39. Pal GK, Ganesh V, Karthik S, Nanda N, Pal P. The effects of short-term relaxation therapy on indices of heart rate variability and blood pressure in young adults. Am J Health Promot 2013 [Epub ahead of print].