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ORIGINAL ARTICLE

Sympathovagal Imbalance in Prehypertension Status

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Background: Heart rate variability (HRV) had been promoted for longer than half a century to monitor the activity of autonomic nerve systems. Previous studies have not clarified the relationship between HRV and prehypertension (pre-HTN) status compared with the normal group. We aimed to figure out the optimal model or cutoff point for predicting the possible pre-HTN status. **Patients and Methods:** We retrospectively collected and reviewed 2586 Asian people who had joined annual physical examination in Tri-Service General Hospital at 2013. The patient profiles such as age, gender, body height, body weight, body weight index, waist circumferences, and serological biochemistry data were analyzed and correlated with HRV parameter. **Results:** A total number of 909 patients were enrolled in our study. The physical stress index (PSI) owed a small but most significant Spearman's relation coefficient ($r = 0.118$, $P < 0.001$) among the other HRV parameters. Statistical significant parameters exist between the normal blood pressure group and pre-HTN group other than gender factor. The measured blood pressure increased with elevated PSI level. A PSI level ≥58.4 has a significant β coefficient in each linear regression model for systolic blood pressure and diastolic blood pressure with a $P < 0.001$ for trend. **Conclusion:** The PSI level gains a positive correlation to elevated blood pressure. Our study emphasized that PSI is an efficient HRV parameter which represents higher risks for pre-HTN status and elevated blood pressure while the PSI level is >58.4. Early intervention to these participants may decrease cardiovascular events in the coming future.

Key words: Heart rate variability, prehypertension, physical stress index

INTRODUCTION

Heart rate variability (HRV) analysis is an effective, sensitive, and noninvasive tool which is widely utilized in evaluating and monitoring the activity of autonomic nerve system (ANS). The previous study raised by G. K. Pal has revealed that the sympathovagal imbalance presented with a proportionate augmenting activity of sympathetic tone and inhibiting vagal activity in prehypertension (pre-HTN) populations.[1,2] Nevertheless, to our knowledge, there are only a few studies focused on the relationship between the HRV parameters and pre-HTN status and especially normal blood pressure (NBP) population.[1-4] The main purpose of our study is to clarify the role of HRV parameters for predicting the possible pre-HTN status and provides clinical information toward the population at risks.

PATIENTS AND METHODS

Inclusion and exclusion criteria of patients

This study aimed at the relationship between the HRV parameters and the blood pressure. People who were enrolled

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in our study were composed of participants receiving the annual physical examination in a single medical center. The participants enrolled in our study should fulfill the HRV tests during annual physical examination. The pre-HTN status was defined as the systolic blood pressure (SBP) elevated higher than 120 mmHg but below 140 mmHg or diastolic blood pressure (DBP) higher than 80 mmHg but lower than 90 mmHg. The NBP was defined as SBP ≤120 mmHg and DBP ≤80 mmHg. Those people who have SBP ≥140 mmHg or DBP ≥90 mmHg had met the exclusion criteria. The participants who have received antihypertensive medication or stated to have a history of hypertension were also excluded. Otherwise, all of the participants were included. We collected blood cell analysis, biochemistry profiles such as blood urea nitrogen, creatinine, aspartate transaminase, alanine transaminase, albumin, uric acid, lipid profiles, and total and direct bilirubin level.

Ethics issue and conflicts of interest

This study had been approved by the Ethics Committee and the Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C. (the TSGH-IRB approval number: 103-05-106). The optimal benefits of all of the populations who were involved in this study did not get damaged, and the risks on the hazard to the patients were similar with people who were not included in our study. The authors claimed that there were no conflicts of interest in this study.

Heart rate variability analysis

All of the participants were asked to rest and relax in a private, quiet room with air condition for 5–10 min in seated position. Room temperature was limited to 22–24°C (71.6–75.2°F). Five minutes electrocardiogram was performed (with SA-3000P; Medicore Co., Ltd., Korea) from 8:00 am to 12:00 am to avoid diurnal fluctuation bias of heart rate and blood pressure. The signal was digitized and analyzed automatically. The time domain and frequency domain analysis were applied. Parameters in time domain analysis includes mean heart rate (mean-HRT), standard deviation (SD) of all normal to normal intervals index (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (R-MSSD), and physical stress index (PSI) an indicator of load on ANS system. The PSI is calculated by the age-related stress value minus the actual level of stress value. The frequency domain analysis includes total power, power in low-frequency (LF, 0.04–0.15 Hz), power in high-frequency (HF, 0.15-0.45 Hz), and the ratio of power in LF/HF using fast Fourier transform. Premature heart beat was automatically ignored during HRV spectral analysis.

Statistics tool

We choose Statistical Product and Service Solutions (SPSS) software (version 17.0; SPSS, Chicago, IL, USA) for analysis. Descriptive data were demonstrated as mean ± SD and ranges. The Chi-square test was used for comparing categorical variables. The analysis of variance (ANOVA) test was used for comparing categorical variables and continuous variables. The Spearman's correlation score was used for ranking the correlations. The multiple regression analysis was applied for rectifying the statistical significant parameters. The P values < 0.05 were defined as statistically significant. All of the covariates that reached statistically significant were recorded and analyzed in each model.

RESULTS

Total 2586 participants were retrospectively reviewed in our study. After administrating the exclusion criteria, a number of 909 participants with NBP or pre-HTN status were included for further analysis. As our prediction before analysis, gender effect played an important role in mean age, body mass index (BMI), waist circumference, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and serum albumin level with $P < 0.001$ except fasting glucose ($P = 0.005$) and total cholesterol level ($P = 0.267$) [Table 1]. The NBP and pre-HTN subgroup also have a significant difference in mean age, BMI, waist circumference, fasting glucose level, and lipid profiles in both male and female population [Table 1]. All of the participants have received HRV analysis using 5 min protocol during annual physical examination. We applied the Spearman's correlation tests for HRV parameters and pre-HTN status or NBP status [Table 2]. Of all the interested HRV parameters, the PSI obtained a small but significant Spearman's relation coefficient to NBP or pre-HTN status ($r = 0.118$, $P < 0.001$) and also had a greatest relation coefficient with SDNN level among all of the HRV parameters ($r = -0.488$, $P < 0.001$). Although the other parameters of HRV are correlated with each other, after we applied the Spearman correlation test, the most significant parameter positively related with pre-HTN or NBP status is PSI. On the other hand, the PSI is the only significant HRV parameters of pre-HTN status after we diminished the sexual difference.

We separated the PSI into four groups according to the quartile of PSI (quartile 1, Q1: PSI ≤ 19.9855; quartile 2, Q2: 19.9855 < PSI ≤ 33.5270; quartile 3, Q3: 33.5270 < PSI ≤ 58.3995; and quartile 4, Q4: PSI > 58.3995). Patient profiles (age, body height, body weight, BMI, SBP, DBP, and waist circumference), serological biochemistry examinations (total cholesterol, triglyceride, HDL, LDL, serum albumin level, fasting glucose, and uric acid), and HRV parameters (mean-HRT, SDNN, R-MSSD, LF,

Table 1: Characteristics of participants with normal blood pressure or prehypertension status, divided by gender

Variables	Male (*n*=574)			Female (*n*=335)			*P*
	NBP (*n*=268)	Pre-HTN (*n*=306)	*P*	NBP (*n*=229)	Pre-HTN (*n*=106)	*P*	
Patient profile, mean±SD							
Age (years)	41.07 (13.43)	45.29 (14.42)	<0.001***	43.62 (11.37)	52.71 (10.94)	<0.001***	<0.001***
BMI (kg/m^2)	24.13 (3.09)	25.74 (4.27)	<0.001***	21.85 (2.94)	23.57 (3.58)	<0.001***	<0.001***
SBP (mmHg)	108.55 (7.25)	125.58 (7.14)	<0.001***	103.48 (9.36)	125.72 (7.87)	<0.001***	<0.001***
DBP (mmHg)	69.48 (6.10)	79.62 (6.16)	<0.001***	66.51 (7.08)	80.47 (5.30)	<0.001***	<0.001***
Waist circumference (cm)	81.87 (8.43)	86.38 (9.05)	<0.001***	74.02 (7.91)	76.76 (9.09)	0.005	<0.001***
Serological data, mean±SD							
Total cholesterol (mg/dL)	190.58 (34.19)	200.51 (36.90)	0.001**	189.61 (37.04)	200.69 (33.95)	0.009**	0.267
Triglyceride (mg/dL)	125.75 (95.29)	153.87 (109.97)	0.001**	99.24 (63.63)	142.34 (180.30)	0.001**	<0.001***
HDL (mg/dL)	52.87 (14.36)	50.03 (13.16)	0.014*	65.99 (15.94)	60.12 (15.96)	0.002**	<0.001***
LDL (mg/dL)	127.06 (32.37)	135.97 (35.08)	0.002**	117.26 (32.64)	128.51 (34.27)	0.004**	<0.001***
Serum Albumin (mg/dL)	4.66 (0.22)	4.66 (0.25)	0.838	4.50 (0.25)	4.52 (0.24)	0.419	<0.001***
Fasting Glucose (mg/dL)	92.63 (18.50)	96.94 (21.39)	0.011*	88.09 (8.61)	97.82 (28.04)	<0.001***	0.005
HRV parameters, mean±SD							
Mean-HRT (bpm)	68.35 (9.83)	70.05 (10.17)	0.042*	68.67 (9.67)	71.09 (9.40)	0.032*	0.792
SDNN (ms)	48.63 (22.27)	44.03 (21.82)	0.013*	40.78 (15.81)	37.70 (30.24)	0.222	<0.001***
R-MSSD (ms)	32.96 (19.88)	30.59 (21.33)	0.172	31.90 (14.04)	26.60 (14.23)	0.002**	0.249
PSI	41.27 (52.96)	52.82 (63.08)	0.019*	46.18 (40.25)	74.06 (105.21)	<0.001***	0.079
LF (ms^2)	738.54 (1082.11)	625.41 (923.39)	0.177	362.72 (546.24)	277.16 (377.73)	0.146	<0.001***
HF (ms^2)	331.29 (378.71)	341.42 (498.22)	0.786	303.33 (271.93)	253.93 (303.17)	0.137	0.071
LF/HF (%)	3.07 (4.64)	2.52 (3.23)	0.097	1.47 (1.57)	1.56 (1.84)	0.642	<0.001***
Categorical variables, *n* (%)							
Metabolic syndrome	58 (21.6)	64 (20.9)	0.832	32 (14)	24 (22)	0.048*	N/A
Smoker	97 (36.2)	98 (32.0)	0.293	13 (5.7)	8 (7.6)	0.995	N/A
Family history	71 (26.5)	86 (28.1)	0.666	96 (41.9)	31 (29.5)	0.058	N/A

*P<0.05, **P<0.01, and ***P<0.001. Metabolic syndrome is defined with patient obtained three or more of the feature mentioned below: (1) Triglyceride ≥150 mg/dL, (2) fasting glucose ≥100, (3) SBP ≥135 mmHg or DBP ≥85 mmHg, (4) HDL <40 mg/dL in male or HDL <50 mg/dL in female, and (5) waist circumference ≥90 cm in male or waist circumference ≥80 cm in female. Smoker is defined with as current smoker or those who quit smoking for less than one year. Family history was defined as hypertension and was diagnosed within the first or second degree relatives of the participant. NBP = Normal blood pressure; Pre-HTN = Prehypertension; SD = Standard deviation; BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HD = High-density lipoprotein; LDL = Low-density lipoprotein; and N/A = Not available

HF, and LF/HF) were analyzed using ANOVA tests [Table 3]. The variables such as age, body height, SBP, DBP, total cholesterol, triglyceride, LDL, serum albumin, fasting glucose, and all of the HRV parameters except LF/HF were statistically significant with a $P < 0.001$. No statistical difference was observed in waist circumference, body weight, and BMI. Among the HRV parameters, the measured PSI and mean-HRT increased with elevated SBP or DBP level while all the other parameters such as SDNN, R-MSSD, LF, HF ($P < 0.00001$), and LF/HF ($P < 0.01$) obtained a negative correlation with PSI level. On the other hand, in this study, the PSI level increased gradually to age, SBP, and DBP, which is indicative that these parameters correlated with each other.

The previously mentioned parameters were rectified using linear regression [Table 4] except other HRV parameters due to the strong relationship with PSI to avoid collinearity in the linear regression model. The dependent variables were designated as SBP and DBP. The regression model was set up using these independent categorical variables with Model 1: PSI quartiles, age, sex, and body height; Model 2: Model 1 + serum albumin level, uric acid, total cholesterol, and LDL; Model 3: Model 2 + metabolic syndrome components (triglyceride, HDL, and fasting glucose). The β coefficient of PSI Q4 was significant in model 1 to model 3 with $P < 0.01$ in SBP and DBP. The P values for trend were also statistically significant in all regression models for both SBP and DBP.

Table 2: The Spearman's coefficient between heart rate variability parameters and prehypertension status or normal blood pressure

	BP	Mean-HRT	SDNN	R-MSSD	PSI	LF	HF	LF/HF
BP	1.000							
Mean-HRT	0.075*	1.000						
SDNN	−0.106**	−0.345	1.000					
R-MSSD	−0.137	−0.528	0.779	1.000				
PSI	0.118	0.484	−0.950	−0.836	1.000			
LF	−0.047†	−0.174	0.768	0.603	−0.733	1.000		
HF	−0.097†	−0.330	0.738	0.873	−0.761	0.612	1.000	
LF/HF	0.035†	0.124	0.180	0.140	−0.119	0.563	−0.251	1.000

†P>0.05, *P<0.05, and **P<0.01. [a]BP: A categorical variable represented either prehypertension status or normal blood pressure. The P value of each Spearman's coefficient mentioned in Table 2 is all <0.001 unless elsewhere specified. Mean-HRT = Mean heart rate; SDNN = Standard deviation of all normal to normal intervals index; R-MSSD = The square root of the mean of the sum of the squares of differences between adjacent NN intervals; LF = Power in low-frequency; HF = Power in high-frequency; and Pre-HTN = Prehypertension

Table 3: The physical stress index was separated into four groups by quartile of physical stress index

Variables (n=909)	PSI quartile 1 (n_1=227)	PSI quartile 2 (n_2=228)	PSI quartile 3 (n_3=227)	PSI quartile 4 (n_4=227)	P
Patient profile, mean±SD					
Age (years)	38.01 (12.97)	42.05 (12.73)	45.26 (11.55)	52.66 (12.11)	<0.00001***
Body height (cm)[a]	169.42 (8.05)	167.60 (8.97)	165.08 (9.31)	164.55 (8.93)	<0.00001***
SBP (mmHg)	113.54 (12.88)	113.87 (12.57)	114.44 (11.99)	118.19 (12.46)	0.00016***
DBP (mmHg)	71.18 (9.05)	72.93 (8.10)	73.65 (8.82)	75.95 (7.98)	<0.00001***
Body weight (kg)[a]	69.31 (13.39)	67.18 (13.91)	68.22 (42.12)	66.52 (14.57)	0.63314
BMI (kg/m^2)	24.01 (3.60)	23.77 (3.59)	23.88 (3.44)	24.47 (4.62)	0.22607
Waist circumference (cm)	80.53 (10.24)	80.49 (9.53)	80.26 (9.60)	80.81 (9.90)	0.23340
Serological exams, mean±SD					
Total cholesterol (mg/dL)	190.91 (33.06)	188.64 (33.87)	195.89 (37.49)	204.03 (38.16)	0.00002***
Triglyceride (mg/dL)	108.09 (55.67)	125.44 (112.62)	148.13 (156.23)	140.26 (82.90)	0.00047***
HDL (mg/dL)	57.54 (14.12)	56.90 (16.75)	53.48 (15.79)	56.33 (16.72)	0.03496*
LDL (mg/dL)	124.30 (33.42)	121.28 (31.24)	129.04 (35.38)	136.44 (35.26)	0.00001***
Serum albumin (mg/dL)	4.69 (0.26)	4.60 (0.26)	4.60 (0.24)	4.54 (0.24)	<0.00001***
Fasting glucose (mg/dL)	90.06 (12.73)	91.71 (11.35)	92.45 (17.37)	99.95 (29.43)	<0.00001***
Uric acid	6.28 (1.59)	6.02 (1.59)	5.81 (1.50)	5.91 (1.51)	0.00823**
HRV parameters, mean±SD					
Mean-HRT (bpm)	63.14 (6.90)	68.23 (8.10)	70.90 (9.97)	75.02 (10.26)	<0.00001***
SDNN (ms)	68.95 (20.43)	45.83 (6.42)	35.28 (5.53)	25.24 (20.30)	<0.00001***
R-MSSD (ms)	51.32 (23.73)	31.91 (8.92)	24.76 (6.53)	16.61 (6.31)	<0.00001***
LF (ms^2)	1289.50 (1372.17)	523.99 (500.47)	281.95 (246.04)	112.60 (111.55)	<0.00001***
HF (ms^2)	678.46 (601.74)	312.16 (204.45)	197.08 (129.59)	86.87 (71.20)	<0.00001***
LF/HF (%)	2.84 (4.49)	2.53 (3.72)	2.04 (2.61)	1.82 (1.95)	0.00459**
Categorical variables, n (%)					
Pre-HTN	91 (40.1)	94 (41.2)	100 (44.1)	127 (55.9)	0.00219**

*P<0.05, **P<0.01, and ***P<0.001. PSI = Physical stress index; SD = Standard deviation; BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; mean-HRT = Mean heart rate; SDNN = Standard deviation of all normal to normal intervals index; R-MSSD = The square root of the mean of the sum of the squares of differences between adjacent NN intervals; LF = Power in low-frequency; HF = Power in high-frequency; LF/HF = Ratio of power in low frequency and high frequency; and Pre-HTN = Pre-hypertension status. Data were lost at body height and body weight column in one participant and replaced by the average of body height and body weight respectively for analysis

Table 4: Physical stress index in quartile as a categorical coefficient of regression models predicting systolic and diastolic blood pressure

Variables	Model 1		Model 2		Model 3	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Dependent variable: Systolic blood pressure						
PSI quartile 1	−1.428 (−3.287-0.432)	0.132	−1.636 (−3.475-0.203)	0.081	−1.306 (−3.135-0.523)	0.162
PSI quartile 2	−1.007 (−2.793-0.779)	0.269[a]	−0.704 (−2.477-1.070)	0.436	−0.519 (−2.266-1.228)	0.560
PSI quartile 3	−0.056 (−1.846-1.734)	0.951[a]	−0.137 (−1.907-1.634)	0.879	−0.504 (−2.271-1.262)	0.575
PSI quartile 4	2.693 (0.799-4.586)	0.005**	2.661 (0.785-4.538)	0.005**	2.522 (0.659-4.385)	0.008**
P for trend	0.00535**		0.00449**		0.01498*	
Dependent variable: Diastolic blood pressure						
PSI quartile 1	−2.488 (−3.767-−1.209)	<0.001***	−2.588 (−3.861-−1.315)	<0.001***	−2.207 (−3.471-−0.944)	<0.001***
PSI quartile 2	−0.221 (−1.215-1.257)	0.726[a]	0.021 (−1.215-1.257)	0.974	0.138 (−1.075-1.352)	0.823
PSI quartile 3	0.666 (−0.573-1.905)	0.292[a]	0.566 (−0.667-1.800)	0.368	0.161 (−1.066-1.388)	0.797
PSI quartile 4	2.093 (0.783-3.403)	0.002**	2.043 (0.736-3.349)	0.002**	1.964 (0.671-3.256)	0.003**
P for trend	<0.00001***		<0.00001***		0.00012***	

*P<0.05, **P<0.01, and ***P<0.001. [a]The P value of ANOVA test for the regression model is higher than 0.05. Model 1=PSI quartiles + age, sex, and body height; Model 2=Model 1 + serum albumin level, uric acid, total cholesterol, and low-density lipoprotein (other serological exams); Model 3=Model 2 + triglyceride, high-density lipoprotein, and fasting glucose (metabolic component). PSI = Physical stress index; and ANOVA = Analysis of variance

DISCUSSION

In this study, we investigated an annual physical examination sample of adults in the Asian population to determine whether there is an association between HRV parameters and pre-HTN status. We reported the PSI level is an efficient HRV parameter which represents a positive correlation to elevated blood pressure. Prior studies showed that the ANS plays an important role in physiological regulation such as blood pressure, heart rate, salivation, function of gastrointestinal tract, endocrine system, and urination.[1-5] The ANS is composed of sympathetic nerve system (SNS) and parasympathetic system. Once if the sympathovagal imbalance occurred, the ability of spontaneous heart rate regulation alters and the interval of successive heartbeat fluctuates. The descriptive method for this phenomenon is nominated as HRV. The standard of measuring HRV is promoted in the early 1990s.[6] There are two methods used for HRV analysis: The time domain and the frequency domain. Previous studies have revealed that HRV parameters were associated with increased cardiovascular risks, especially in hypertension population.[3,4] Meanwhile, the decreased HRV has also related with higher risks of cardiovascular invents.[7,8] Another study has stated that decreased preanesthesia HRV and increased postoperative troponin-I level are a strong and independent predictor of postoperative 1 year mortality rate for noncardiac surgery in high-risk patients of coronary artery disease.[9] However, few studies have examined an association between the HRV parameters and pre-HTN status and especially NBP population.[1-4] The current study represents the first survey-based analysis to demonstrate evidence of an association between HRV parameters and pre-HTN status.

The gender effect plays an important role in the physiological and pathological discrepancy. In both male group and female group, not only physical profiles (age, BMI, SBP, DBP, and waist circumference) but also serological data had a statistical significant difference ($P < 0.001$). After we diminished the gender effect, the NBP group and pre-HTN group were still different in parameters including age, BMI, waist circumference, lipid profiles, and fasting glucose level in both male and female population with $P < 0.05$ at least. It raised our concern that let alone the sex factor, even pre-HTN status might relate to several physiological and serological differences.

There were many subjective quantification scales for describing the grade of physical stress such as the social readjustment rating scale, model, and job stress questionnaire.[10-12] The stress theory promoted by Hans Selye in the early 1960s stated that the increased psychological stress has related with physiological abnormality caused by hypothalamic-pituitary-adrenal axis, which was also nominated as a general adaption syndrome: The elevated physical stress enhances the activity of SNS, increases secretion of catecholamine or glucocorticoid, and promotes the activation of stress response.[13,14] The HRV analysis offers an effective and objective scale to record and describe the activity of ANS, which directly influences and modulates the blood pressure.

The body inflammation reaction controlled by the central nervous system mediates the physiological response to

environmental stress or pathological cardiovascular sequelae. Previous studies have revealed the relationship between HRV and inflammation process in coronary artery disease and metabolic syndrome with glucose tolerance impairment.[15,16] Decreased HRV is also considered to have higher risks of cardiovascular events.[9] Hamaad *et al*. have found that the SDNN, LF, and very LF power obtained negative correlation with the white cell counts, high sensitivity C-reactive protein (CRP), and interleukin-6 level in patients proven to be an acute coronary syndrome.[17] The other studies claimed that the CRP level has negative correlation between all of the HRV parameters in patients admitted due to acute unstable angina.[18]

Upon all of the HRV parameters in this study, the PSI level obtained the highest correlation efficient with pre-HTN or NBP status. The mean-HRT has a positive correlation and the SDNN, R-MSSD, LF, HF ($P < 0.001$), and LF/HF ($P < 0.01$) have a negative correlation with PSI level in the focused participants. It is well documented that the SDNN level <70 ms brought on a higher multivariate risk of cardiac death after an acute myocardial infarction, and the SDNN <65.3 ms had an increased risk of sudden death in patients admitted due to congestive heart failure.[19,20] Every ten milliseconds increase in SDNN offered a 20% decrease risk of mortality in chronic congestive heart failure.[19] After we allocated these participants according to the PSI level, the mean SDNN level is lower than 65 at PSI Q2 to Q4 significantly, which is an indicator of poor prognostic factor for cardiovascular event.

Meanwhile, we demonstrated that some of the metabolic components other than blood pressure had an increasing or decreasing trend of mean value accompanied with increased PSI level. The interested metabolic components include serum glucose level, HDL, TG, and waist circumference. The waist circumference has been proven that there is no statistically difference between PSI Q1 to Q4. The mean blood sugar increased with elevated PSI level, which can be considered as the effect of glucocorticoid release accompanied with the increased physical stress. In the study promoted by Sajadieh *et al*., the SDNN level was negatively correlated with inflammatory biomarkers, serum blood sugar, and TG level in population without obvious heart disease.[21] As a result, the PSI level correlated positively with inflammatory indices and the increasing sympathetic activity. The trend of mean HDL decreased from PSI Q1 to Q3 and had a mild increase at PSI Q4, which is opposite to the trend of TG level. The possible causes are still unclear, but this result is suggestive that maybe the optimal cut-point of the upper normal limit of PSI is not perfectly to quartile level in this study.

Furthermore, we set up the regression model for each PSI quartile and using the statistically significant parameters as independent variables to predict the SBP or DBP level (dependent variables) after the ANOVA tests. When the measured average PSI level is higher than 58.4, the PSI level becomes a significant independent variable in the linear regression models. This result is indicative that the PSI level higher than 58.4 promotes the increasing blood pressure and owes a significant risk of cardiovascular events.

Finally, the limitation of this study is that our studies checked spotting blood pressure. Although all of the participants are asked to rest for 5–10 min to minimize the bias, the fluctuation of blood pressure may be influenced by the biopsychosocial status at that moment. Second, according to the standards of measurement of HRV, parameters in frequency domain includes short-term and long-term (24 h) analysis.[6] The long-term recording spectral analysis of HRV parameters was not available in our study. Further, the effect on HRV analysis of other comorbidity such as diabetes mellitus, metabolic syndrome, increased peripheral vessel resistance, and cardiopulmonary disease had not been completely excluded. More large-scale, prospective, randomized control studies are needed to clarify these issue.

CONCLUSION

In our study, the elevated PSI level obtained from the HRV analysis has related with increased blood pressure even in patients without hypertension. The PSI level >58.4 is a significant independent variable in our regression models to predict the SBP and DBP level. Early intervention in this population may be associated with the decreasing incidence of ongoing cardiovascular events.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Pal GK, Adithan C, Amudharaj D, Dutta TK, Pal P, Nandan PG, *et al*. Assessment of sympathovagal imbalance by spectral analysis of heart rate variability in prehypertensive and hypertensive patients in Indian population. Clin Exp Hypertens 2011;33:478-83.
2. Pal GK, Amudharaj D, Pal P, Saranya K, Lalitha V,

Gopinath M, *et al.* Study of sympathovagal imbalance by spectral analysis of heart rate variability in young prehypertensives. Indian J Physiol Pharmacol 2011;55:357-63.
3. Pal GK, Adithan C, Ananthanarayanan PH, Pal P, Nanda N, Durgadevi T, *et al.* Sympathovagal imbalance contributes to prehypertension status and cardiovascular risks attributed by insulin resistance, inflammation, dyslipidemia and oxidative stress in first degree relatives of type 2 diabetics. PLoS One 2013;8:e78072.
4. Pal GK, Pal P, Lalitha V, Amudharaj D, Nanda N, Dutta TK, *et al.* Increased vascular tone due to sympathovagal imbalance in normotensive and prehypertensive offspring of hypertensive parents. Int Angiol 2012;31:340-7.
5. McCorry LK. Physiology of the autonomic nervous system. Am J Pharm Educ 2007;71:78.
6. 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. Eur Heart J 1996;17:354-81.
7. Kleiger RE, Miller JP, Bigger JT Jr., Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256-62.
8. Kupari M, Virolainen J, Koskinen P, Tikkanen MJ. Short-term heart rate variability and factors modifying the risk of coronary artery disease in a population sample. Am J Cardiol 1993;72:897-903.
9. Filipovic M, Jeger R, Probst C, Girard T, Pfisterer M, Gürke L, *et al.* Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. J Am Coll Cardiol 2003;42:1767-76.
10. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. J Psychosom Res 1967;11:213-8.
11. Williams S, Cooper CL. Measuring occupational stress: Development of the pressure management indicator. J Occup Health Psychol 1998;3:306-21.
12. Kawada T. Relationship between components of the metabolic syndrome and job strain using a brief job stress questionnaire (BJSQ). Int Arch Occup Environ Health 2013;86:725-6.
13. Russell GM, Kalafatakis K, Lightman SL. The importance of biological oscillators for hypothalamic-pituitary-adrenal activity and tissue glucocorticoid response: Coordinating stress and neurobehavioural adaptation. J Neuroendocrinol 2015;27:378-88.
14. Selye H. Stress and the general adaptation syndrome. Br Med J 1950;1:1383-92.
15. Phillips AN, Neaton JD, Cook DG, Grimm RH, Shaper AG. Leukocyte count and risk of major coronary heart disease events. Am J Epidemiol 1992;136:59-70.
16. Brunner EJ, Hemingway H, Walker BR, Page M, Clarke P, Juneja M, *et al.* Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: Nested case-control study. Circulation 2002;106:2659-65.
17. Hamaad A, Sosin M, Blann AD, Patel J, Lip GY, MacFadyen RJ. Markers of inflammation in acute coronary syndromes: Association with increased heart rate and reductions in heart rate variability. Clin Cardiol 2005;28:570-6.
18. Lanza GA, Sgueglia GA, Cianflone D, Rebuzzi AG, Angeloni G, Sestito A, *et al.* Relation of heart rate variability to serum levels of C-reactive protein in patients with unstable angina pectoris. Am J Cardiol 2006;97:1702-6.
19. Bilchick KC, Fetics B, Djoukeng R, Fisher SG, Fletcher RD, Singh SN, *et al.* Prognostic value of heart rate variability in chronic congestive heart failure (veterans affairs' survival trial of antiarrhythmic therapy in congestive heart failure). Am J Cardiol 2002;90:24-8.
20. 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.
21. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Abedini S, Hansen JF. Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. Eur Heart J 2004;25:363-70.