Original Article

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Association of High Blood Pressure with Heart Rate Variability in Children

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Abstract

Objective: To determine the association between heart rate variability (HRV) and hypertension in Chinese children.

Methods: The study was conducted in First Hospital of Jilin University, China. A total of 101 children were recruited in this study. They were divided into a high systolic blood pressure (SBP) group (HS group) and normal SBP group (NS group) according to the SBP levels. In the second set of experiments, the children were divided into a high diastolic blood pressure (DBP) group (HD group) and normal DBP group (ND group) according to the DBP levels. HRV measurements were performed, and the time domain and power spectrum values were calculated.

Findings: The differences of low frequency (LF)/high frequency (HF) ratio, HF, and standard deviation of normal-to-normal RR intervals (SDNN) between daytime and nighttime were obviously abolished in HS and HD groups. The HS group displayed significantly lower values of HRV over a 24 h period compared to the NS group (SDNN, standard deviation of the averaged normal-to-normal RR intervals [SDANN], Triangle Index, root mean square successive difference [RMSSD], total power [TP], ultra-LF [ULF], and HF). Only the Triangle Index in the HD group was lower than that in ND group.

Conclusion: We provide evidence that HRV is reduced and the circadian rhythm of HRV is weakened in hypertensive children, and hypothesize that a reduced HRV is a potential pathophysiological mechanism linking childhood hypertension and adulthood cardiovascular diseases.

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Key Words: Heart Rate; Blood Pressure; Hypertension; Children

Introduction

Coronary heart disease (CHD) and cerebrovascular disease (CVD) represent the most common causes of death worldwide. It has been well-established that one of the most important causes of CHD and CVD is hypertension, which creates a major economic burden in various countries throughout the world[1]. Childhood hypertension has become a widely investigated topic within the last decade due to its rising prevalence and associated sequelae[2]. Due to blood pressure (BP) tracking, which is described as “a phenomenon when a BP level early in life predicts a BP level later on”, childhood hypertension has been thought to be tightly associated with adulthood hypertension[3]. The American Heart Association (AHA) guidelines state the importance of preventing atherosclerotic cardiovascular disease beginning in hypertensive children[4]. Thus, childhood hypertension is a key risk factor of CHD and CVD in adulthood[2].

Heart rate variability (HRV), which is measured as variation in the beat-to-beat interval, is a

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physiological phenomenon where the time interval between heart beats varies. During the last two decades, HRV has been extensively studied and represents one of the most promising markers for cardiac autonomic nerve function. The noninvasiveness and easy derivation of the HRV measurement make it more practical and widely studied. Measures of HRV in both the time and frequency domains have been used successfully to index cardiovascular autonomic nervous function activity. A large number of studies have demonstrated that HRV is associated with cardiovascular diseases and mortality[5-7]. Hypertension is commonly associated with increased sympathetic activity and decreased parasympathetic activity. Reduced HRV has been previously reported in adulthood hypertension[8]. Recently, reduced HRV was observed in salt-sensitive men[9], and negatively correlated with the prolonged QT interval in patients with uncomplicated essential hypertension[10]. However, the association between childhood hypertension and HRV is largely unknown. Moreover, reliability of findings in adults may not be generalized to younger individuals and children due to age-dependent differences in autonomic functioning[11]. Thus, the aim of this study was to explore the possible association between HRV and BP levels in children

Subjects and Methods

Selection of study participants

A total of 150 healthy children in a primary school receiving routine physical examination in the First Hospital of Jilin University from January 2010 to August 2010 were recruited for the study, which took place at the same hospital. Informed consent was obtained from parents and participants prior to testing. The study was approved by the ethical committees of Jilin University. After obtaining a history, physical examination, and series of additional examinations, including myocardial enzyme assays, routine analysis of blood, cardiac color ultrasonography, chest radiography, and resting electrocardiogram, 105 healthy children between the ages of 9 and 11 years were chosen. 'Healthy' was defined as being free of any major cardiovascular or metabolic disease diagnoses, such as diabetes, arrhythmia, orthostatic intolerance, unexplained syncopal episodes, and obstructive sleep apnea. After a Holter examination, 49 of the subjects were excluded because of arrhythmias (18 children with occasional atrial premature beats, 20 children with occasional premature ventricular contractions, and 11 children with first-degree atrioventricular block). A total of 101 children (58 males and 43 females) subsequently entered the study. Based on the SBP levels, 28 children (19 males, 9 females) entered the HS group, while the other 73 children (39 males, 34 females) entered the NS group. Based on the DBP levels, 23 children (12 males, 11 females) entered the HD group and the other 78 children (46 males, 32 females) entered the ND group.

Blood pressure measurement and grouping

The height, body weight, waist line, and hip circumference of the subjects were measured. The systolic BP (SBP) and diastolic BP (DBP) were measured and recorded 3 times with a mercury sphygmomanometer on the right arm after the children had rested for 30 minutes. The average values obtained were recorded as the BP. According to the criteria for child hypertension by the National High Blood Pressure Education Program of the USA[12] and the distribution tendency of hypertension in Chinese children[13], the children were divided into a high SBP group (HS) and a normal SBP group (NS) based on SBP levels. The children with normal SBP in this study were defined as children with an average SBP less than the 90th percentile for gender, age, and height. The children with high SBP were defined as children with an average SBP greater than or equal to the 90th percentile for gender, age, and height.

In another set of experiments, the same children were divided into a high DBP group (HD) and a normal DBP group (ND) according to their DBP levels. The normal DBP and high DBP were defined similarly as the SBP.

HRV analysis

For the HRV parameters, the Triangle Index, standard deviation of normal-to-normal RR intervals (SDNN), and total power (TP) reflected the total variability of HRV. The power of ultra low frequency (ULF <0.003 Hz), low frequency (LF 0.04-0.15 Hz), and standard deviation of the averaged normal-to-normal RR intervals (SDANN) were primarily sympathetic effects on cardiac autonomic function, while high frequency (HF 0.15-0.40 Hz) was mediated primarily by parasympathetic innervation of the heart[14]. Moreover, the root mean square successive difference (rMSSD) and the RR intervals greater than 50 ms (PNN50) were also useful indices of parasympathetic activity, and the LF/HF ratio indicated the balance of sympathetic and parasympathetic nervous modulation[14].

HRV measurements were performed as previously described[15]. The participants did not receive medication for 1 week prior to the initiation of the study or during the study, and had no coffee or tea before and during the day of examination. The participants slept for more than 8 h and did not watch TV the night before and during the study. They were asked to continue their usual daily activities (avoiding strenuous exercise) before and during the 24 h Holter electrocardiographic recording. Electrocardiograms were obtained using a 24 h ambulatory electrocardiographic recorder (Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, Connecticut, USA)[16]. Each recording began between 08:00-09:00 and lasted 24 h. During the 24 h study, patients followed their usual daily activities.

After the experiment, the analog ECG signal was digitally sampled at 1000 Hz. The digitized ECG data were differentiated, and the length of one cardiac cycle was determined as instantaneous HR (beats/min). These data were then analyzed by the BMS Century 3000 HRV analysis software package (version 5.2). According to a previous study[17], the mean heart rate and the following domain measures of HRV were calculated for daytime (10:00-11:00), nighttime (01:00-02:00), and over a 24 h period: SDNN, RMSSD, PNN50, ULF, LF, HF, and LF/HF ratio. The SDANN, Triangle Index, and TP over a 24 h period were also calculated. The mean RR intervals for daytime and nighttime were also calculated.

Statistical analysis

Values were expressed as mean±standard error for each study group. Independent-samples t test (Gaussian distribution) and Mann-Whitney test[18] (non-Gaussian distribution) were used to compare indexes between groups. Paired-samples t test (Gaussian distribution) and Wilcoxon Signed Ranks Test (non-Gaussian distribution) were used to compare the HRV values between nighttime and daytime. All statistical procedures were performed using SPSS 13.0 (SPSS Inc., Chicago, IL)[19]. An alpha level of 0.05 was used to denote statistical significance.

Findings

Characteristics of the study population

A total of 101 Chinese children were included in the study. As shown in Table 1, there were no differences in age, height, and body weight between the HS group and NS group or between the HD group and ND group. The BMI index (20.15 ±4.59 vs. 17.31±3.36, P<0.01), waist/hip ratio (0.88±0.06 vs. 0.84±0.05, P<0.01), and waistline

Table 1: General characteristics of the study population grouped by blood pressure

Variables	Grouped by SBP			Grouped by DBP		
	HS group (n = 28)	NS group (n = 73)	*P* Value	HD group (n = 23)	ND group (n = 78)	*P* Value
Male/female	19/9	39/34	0.2	12/11	46/32	0.6
Age	10.26(1.69)	10.13 (1.15)	0.8	10.00(1.59)	10.25(1.26)	0.7
Height (cm)	143.8(14.98)	139.44(10.76)	0.6	139.51(14.5)	141.4 (11.6)	0.6
Body weight (kg)	43.32(16.87)	33.76 (8.4)	0.05	38.47(15.99)	36.42(11.24)	0.9
BMI (kg/m²)	20.15(4.59)	17.31 (3.36)	0.008#	18.96(4.1)	18(4.0)	0.3
Waist/hip ratio	0.88(0.06)	0.84 (0.05)	0.006*	0.88 (0.064)	0.85(0.054)	0.2
Waistline height ratio	0.49 (0.07)	0.43 (0.06)	<0.001#	0.47 (0.06)	0.44(0.07)	0.05

The values are mean (standard error). **P* <0.05 HS Group vs. NS Group by independent *t*-test. #*P* <0.05 HS Group vs. NS Group by Mann-Whitney test. HS: high SBP; NS: normal SBP; HD: high DBP; ND: normal DBP; BMI: body mass index height ratio (0.49±0.07 vs 0.43±0.06, *P*<0.001,) in the HS group were significantly higher than those in the NS group, respectively. However, no significant differences in these parameters were observed between HD and ND groups (*P*>0.05).

Comparison of HRV indexes between groups

As shown in Table 2, the HS group displayed significantly lower HRV values over a 24 h period compared to the NS group (SDNN, *P*<0.001; SDANN, *P*<0.001; Triangle Index, *P*<0.001; RMSSD, *P*=0.04; TP, *P*<0.001; ULF, *P*<0.001; and HF *P*=0.04). When the children were divided into two groups (HD and ND groups) based on the DBP levels, only the Triangle Index (*P*=0.04) in the HD group was lower than that in the ND group.

Comparison of HRV indexes between daytime and nighttime

We also compared the HRV indexes between daytime and nighttime in children of the HS, NS, HD, and ND groups. As shown in Table 3, the means of the RR interval (*P*=0.00), SDNN (*P*=0.01), PNN50 (*P*<0.001), and HF (*P*=0.04) during the nighttime in the NS group were higher than those during the daytime; however, the LF/HF (*P*=0.01) ratio was lower. In the HS group, only the means of the RR (*P*<0.001) interval and PNN50 (*P*<0.001) during the nighttime were higher than those during the daytime.

Similar results were observed in the HD and ND groups. In the ND group, the means of the RR interval (*P*<0.001), SDNN (*P*=0.01), PNN50 (*P*<0.001) during the nighttime were higher than those during the daytime; however the LF/HF (*P*<0.001) ratio was lower. In contrast, in the HD group, only the means of the RR interval (*P*<0.001) and PNN50 (*P*<0.001) during the nighttime were higher than those during the daytime.

Discussion

In the present study, we provide evidence that an increased BP level is associated with reduced HRV in Chinese children. Although previous work has

Table 2: HRV parameters and the mean heart rate of the study population grouped by blood pressure

Parameters	Variables	Grouped by SBP		*P* Value	Grouped by DBP		*P* Value
		HS group (n = 28)	NS group (n = 73)		HD group (n = 23)	ND Group (n = 78)	
Parameters reflecting total HRV	Mean HR (beats/min)	89 (10.2)	82.3 (7.8)	<0.001*	86.3 (12.5)	83.9 (7.6)	0.5
	SDNN (ms)	127.9 (28.4)	153.9 (32.9)	<0.001*	144.4 (42.0)	145.4 (30.2)	0.9
	Triangle Index	511.7 (149.9)	658.3 (121.3)	<0.001*	559.9 (159.9)	622.2 (143.5)	0.04†
	TP (ms²/HZ)	8392 (4065)	16275 (5330)	<0.001‡	11316.0 (5837.1)	11184.4 (5163)	0.9
Parameters primarily reflecting parasympathetic activity	rMSSD (ms)	61.4 (26.9)	72.9 (39.4)	0.04‡	70.2 (33.1)	68.8 (27.6)	0.9
	PNN50 (%)	24.6 (14.2)	28.7 (14.2)	0.1	30.7 (17.1)	26.3 (13.0)	0.4
	HF (ms²/HZ)	582.3 (518.9)	750.1 (582.9)	0.04‡	648.7 (479.6)	710.9 (597.9)	0.8
Parameters primarily reflecting sympathetic activity	SDANN (ms)	256.2 (506.1)	265.8 (471.3)	<0.001‡	198.2 (267.6)	156.5 (99.2)	0.8
	ULF (ms²/HZ)	5448 (2904)	7702.4 (634.1)	<0.001‡	6935.6 (3785.8)	6938.5 (493.6)	0.8
	LF (ms²/HZ)	572.8 (283.2)	647.7 (300.6)	0.09	661.5 (329.3)	610.1 (284.4)	0.5
Parameter reflecting the balance of sympathetic and parasympathetic activity	LF/HF	1.3 (0.6)	1.2 (0.5)	0.5	1.3 (0.7)	1.2 (0.5)	0.9

The values are mean±standard error. HS: high SBP; NS: normal SBP; HD: high DBP; ND: normal DBP; HR: Heart Rate; SDNN: standard deviation of normal-to-normal RR intervals; SDANN: standard deviation of the averaged normal-to-normal RR intervals; RMSSD: the root mean square successive difference; PNN50: RR intervals greater than 50 ms; TP: total spectral; ULF: ultra low frequency; LF: low frequency; HF: high frequency; LF/HF: LF-HF ratio. **P* <0.05 HS Group vs. NS Group by unpaired *t*-test. ‡*P*<0.05 HS Group vs. NS Group by Mann-Whitney test. †*P* <0.05 HD Group vs. ND Group by independent *t*-test shown that HRV is reduced in adulthood hypertension[8], the current understanding of HRV in children is not sufficient. In this population-based investigation, we examined HRV variables across the spectrum of normal and abnormal BP levels in children. Our findings extend previous observations of HRV and hypertension in adult hypertensive patients.

HRV is affected by many factors, including gender, age, nervous system diseases, renal failure, diabetes, myocarditis, arrhythmia, food (such as tea and coffee), and exercise. In the present study, there were no significant differences between gender, age, and body weight (Table 1) among the different groups, which excluded the possibility that these factors had an influence on HRV. After the participants were grouped by SBP levels, the HS group (high SBP group) exhibited a high BMI, waist/hip ratio, and waistline height ratio compared to the NS group (normal SBP group).

In children with arterial hypertension, the increase of sympathetic activity during sleep has been shown to significantly correlate with left ventricular mass and a corrected left ventricular mass index[20]. Moreover, HRV can predict the outcome of children with pulmonary arterial hypertension[21]. Urbina et al tested HRV during cardiovascular reactivity testing in 39 male adolescents with high and low blood pressure. They found that the LF/HF ratio was significantly higher and the PNN50 was significantly lower in white adolescents compared to black adolescents[22].

Notably, the authors also reported that there was a trend of a higher LF/HF ratio and lower PNN50 in blacks and whites with higher levels of BP, although this did not reach statistical significance. Unlike their results, our data clearly demonstrate there are significant differences in SDNN, rMSSD, TP, and ULF between the HS and NS groups. However, differences in most of these parameters did not reach statistical significance when the HD and ND groups were compared (Table 2). These data indicate that both parasympathetic activity and sympathetic activity are impaired in hypertensive children. In our opinion, the absence of differences in HRV between the HD and ND groups suggest that the influence of SBP on HRV may be greater than the influence of DBP.

In the NS and ND groups, sympathetic and parasympathetic nervous system modulation existed, which was shown by the significant differences in the means of the RR interval, SDNN, PNN50, HF, and LF/HF ratios between daytime and nighttime. Differences in the LF/HF ratio, HF, and SDNN were clearly abolished in the HS and HD groups, indicating that the circadian rhythm of HRV was impaired (Table 3). This was the most important finding in our study of children shown here. Our data support a previous study that evaluated the contribution of the parasympathetic and sympathetic nervous systems to the diurnal cardiovascular rhythms, which found that neither the sympathetic activity nor parasympathetic activity, at least in isolation, was essential for generating cardiovascular diurnal rhythms in the fetus[23].

Our results explicitly show that increased BP, and particularly SBP, is tightly associated with dysfunction of the autonomic nervous system in children. Christensen et al reported that hypercholesterolemia was associated with a decreased 24 h HRV in men with and without ischemic heart disease[24]. In addition, Liao et al showed that lower HRV was associated with the development of coronary heart disease in individuals with diabetes[25]. Gianaros et al reported that in postmenopausal women, a greater reduction in HRV might be an independent correlate of subclinical atherosclerosis[26]. Recently, more evidence for the relationship of HRV and atherosclerosis in adults has been reported[27-31]. Since it is well accepted that the disease process of atherosclerosis begins in childhood and adolescence, we propose that the chronic stress of hypertension and dysfunction of the autonomic nervous system in children may accelerate atherosclerosis. Thus, dysfunction of the autonomic nervous system and hypertension during childhood may be possible causes of atherosclerosis and atherosclerosis-related disorders during adulthood (i.e., myocardial infarction and ischemic stroke). However, this hypothesis will require additional studies for further analysis. Moreover, there was a strong association between blood pressure and BMI, suggesting that obesity may contribute to this association. Since we cannot exclude this possibility, it may be a limitation of our study.

Table 3: Comparison of HRV parameters observed during the daytime and nighttime in the study population grouped by blood pressure

Group		Total HRV		Parasympathetic activity			Sympathetic activity		Balance of sympathetic and parasympathetic activity
		Mean RR interval	SDNN	RMSSD	PNN50	HF	LF	ULF	LF/HF
HS Group	Day time	616.3 (24.9)	87.1 (32.8)	85.7 (49.5)	18.9 (15.3)	805.4 (2.6)	626.5 (6.5)	548.5 (96.5)	1.2 (0.6)
	Night time	803.5 (21.4)	890.1 (107.6)	76.9 (43.3)	34.4 (23.8)	913.9 (41.8)	546.4 (28.7)	823.9 (348.4)	1.1 (0.5)
	P Value	<0.001 ‡	0.7	0.4	<0.001*	0.8	0.1	0.6	0.1
NS Group	Day time	624.9 (71.8)	100.1 (29.7)	92.9 (44.0)	22.8 (13.7)	1040.9 (935.4)	961.1 (726.2)	862.7 (968.9)	1.2 (0.6)
	Night time	639.4 (73.8)	114.9 (44.4)	99.9 (60.7)	44.5 (26.5)	1375.1 (1379.3)	944.8 (795.6)	1604.4 (6629.3)	0.9 (0.5)
	P Value	<0.001 ‡	0.01*	0.4	<0.001*	0.04*	0.8	0.3	<0.001*
HD Group	Day time	617.2 (75.8)	95.0 (44.8)	87.7 (59.1)	22.5 (17.4)	861.8 (988.9)	794.3 (731.3)	890.2 (1057.3)	1.3 (0.6)
	Night time	835.6 (148.1)	100.0 (25.6)	86.5 (42.1)	41.4 (23.6)	967.7 (796.6)	686.7 (452.8)	558.7 (327.4)	1.1 (0.6)
	P Value	<0.001 ‡	0.5	0.7	<0.001*	0.5	0.5	0.8	0.4
ND Group	Day time	625.7 (81.6)	96.9 (25.2)	92.0 (40.5)	21.5 (13.1)	1017.3 (873.1)	898.5 (650.9)	746.9 (822.1)	1.2 (0.5)
	Night time	876.1 (104.9)	115.5 (50.3)	96.4 (61.4)	41.9 (26.9)	1346.3 (1043.4)	893.9 (806.2)	1682.9 (614.4)	0.9 (0.5)
	P Value	<0.001 *	0.01*	0.6	<0.001*	0.06	0.6	0.07	<0.001 *

The values are mean (standard error). HS: high SBP; NS: normal SBP; HD: high DBP; ND: normal DBP; SDNN: standard deviation of normal-to-normal RR intervals; RMSSD: the root mean square successive difference; PNN50: RR intervals greater than 50 ms; ULF: ultra low frequency; LF: low frequency; HF: high frequency; LF/HF: LF-HF ratio. ‡<0.05 nighttime HRV vs. daytime HRV by paired t-test; **P* <0.05 nighttime HRV vs. daytime HRV by Wilcoxon test

A previous study has shown the presence of an autonomic nervous system dysfunction, and in particular a baroreflex impairment, in both hypertensive and pre-hypertensive children[32]. However, the methodology used in that study was different from what was used in this study. The authors mainly focused on the relationship between spontaneous baroreflex and RR variance. In contrast, we evaluated several other HRV parameters in the current study, including SDNN, SDANN, triangle index, RMSSD, TP, ULF, and HF, which may provide more information regarding HRV dysfunction. Nevertheless, our conclusion is clearly in agreement with the previous study, which suggests that autonomic nervous system dysfunction is a critical feature in hypertensive and pre-hypertensive children.

The major limitation of this study, besides the relatively small number of study participants, was that we did not study the difference between male and female children. There were obvious gender-related differences in animal and human studies[33,43]. Young women have higher day-and nighttime vagal tone than men with similar age range[34]. Therefore, whether the hypertensive girls have similar phenotypes is an interesting issue.

Since dysfunction of the autonomic nervous system is a common complication of childhood hypertension, the early subclinical detection of autonomic dysfunction may be useful for the risk stratification and subsequent management of hypertension in children, and thereby may dictate the aggressiveness of intervention and the choice of therapy in adulthood.

Conclusion

Our data provide evidence that an increased BP level is associated with reduced HRV in children, which may further our understanding of the association of high blood pressure with cardiac autonomic nerve function in children.

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Conflict of Interest: None

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