Heart Rate Variability in Middle-Aged Men with New-Onset Hypertension

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Background: It has been well established that hypertension is associated with autonomic dysregulation. Studies investigating HRV have established that hypertension is characterized by sympathetic overactivity and or attenuation of parasympathetic modulation of the heart.

Methods: We examined short-term heart rate variability (HRV) as well as conventional indices of cardiovascular autonomic function including heart rate variation during deep breathing (HRVdb), 30: 15 ratio, pressor response to quiet standing and isometric handgrip in 35 male subjects (39 ± 7 year, mean ± SD) with new-onset hypertension (resting BP 155 ± 17/101 ± 8 mm Hg) and 17 age-matched normotensive men (resting BP: 111 ± 7/71 ± 5 mmHg).

Results: HRVdb was significantly lower in hypertensives (21 ± 8) compared to normotensives (mean age 36 ± 7, P = 0.03). Differences in mean RR were insignificant, logarithm of high-frequency (HF) spectral power of RR intervals was significantly lower in hypertensives compared to normotensives in the supine position (P = 0.02).

Conclusions: Our data suggest that new-onset hypertension is characterized by diminished short-term HRV, possibly due to an increase in cardiovascular sympathovagal balance.

Ann Noninvasive Electrocardiol 2008;13(3):242–248

autonomic regulation; sympathovagal balance; spectral analysis

INTRODUCTION

Hypertension is a major risk factor for cardiovascular and cerebrovascular disease. Higher the long-term level of blood pressure (BP), greater the chances of myocardial infarction, renal failure, stroke, and heart failure.[1] Clinical hypertension has been defined as a sustained elevation of BP where the benefits of intervention will exceed that of non-intervention.[2]

The autonomic nervous system has been demonstrated to play an important role in the development and maintenance of essential hypertension.[3] Due to its anatomical positioning, it cannot be approached directly; hence, indirect measures have been used in assessing its role in health and disease. Heart rate variability (HRV) is a noninvasive tool used to assess autonomic modulation of SA node in health and disease states like diabetes, hypertension, myocardial infarction, and heart failure.[4]

Essential hypertension is associated with altered cardiovascular autonomic function[3] and studies investigating HRV have established that hypertension is characterized by sympathetic over activity[5] and or attenuation of parasympathetic modulation of the heart.[6] The presence of increased baseline sympathetic activity in hypertension has also been established by direct measurements of muscle sympathetic nerve activity.[7] Virtanen et al.[8] have shown that all measures of short-term HRV are reduced in untreated hypertensives. There is evidence that short-term HRV is reduced in subjects with new-onset hypertension.[9] Reduced HRV has been correlated with increased mortality after acute

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Financial support: *The Indian Council for Medical Research (ICMR) supported this work in the form of Senior Research Fellowship to P. Pavithran.*

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myocardial infarction.[10,11] From India, until now only one study has provided evidence for the presence of an increased sympathetic activity and a decreased parasympathetic activity in patients with recent onset hypertension.[12]

The present study was carried out with the aim of evaluating short-term HRV in patients newly diagnosed to have hypertension and not having taken antihypertensive medication in the past. At the same time, conventional indices of cardiovascular autonomic function were also determined. These are the heart rate variation during timed deep breathing (HRVdb) at 6 breaths/min; the 30:15 ratio during active orthostasis;[13] and the pressor and heart rate (HR) response to 5 minutes of quiet standing and 1 minute sustained isometric handgrip. We tested the hypothesis that short-term HRV is reduced in new-onset hypertension. Secondly, the correlation between conventional indices and short-term HRV indices has also been examined.

MATERIALS AND METHODS

This study was conducted in the Autonomic function laboratory of the Department of Physiology, JIPMER, Pondicherry. Thirty-five patients with new-onset hypertension were recruited from the Medicine Outpatient department of JIPMER hospital. New-onset hypertension was defined as sitting BP $\geq$ 140/90 mmHg on three different occasions and no history of antihypertensive medication. BP was recorded using a mercury sphygmomanometer by the same observer with the subjects comfortably seated for at least 5 minutes. Seventeen normotensive controls with resting systolic pressure (SP) <120 mm Hg and diastolic pressure (DP) <80 mmHg were also recruited. ECG, fasting blood glucose, and lipid profile were obtained at baseline for both hypertensives and controls. Subjects with body mass index (BMI) exceeding 30 kg/m^2 and/or fasting blood glucose >126 mg/dL were excluded from the study. Patients with evidence of target organ damage from high BP, secondary hypertension, and other acute illnesses were excluded. All participants gave written informed consent. The research and ethics committees of JIPMER approved the study protocol. One day prior to the actual recording of BP and autonomic indices, subjects reported to the lab after an overnight fast; 5 mL of venous blood was collected in vials containing ethylene diamine tetra acetic acid. Plasma was separated out and used for analysis. Total cholesterol was analyzed by cholesterol oxidase method;[14] triglycerides (TG) were estimated by glycerol oxidase method; high-density lipoprotein cholesterol (HDL-C) by phosphotungstate magnesium acetate method using reagent kit from Agappe Diagnostics (Maharashtra, India) adapted to 550 Express Plus Random Access Auto-analyzer (West Pole, Germany); and low-density lipoprotein cholesterol (LDL-C) was calculated using Friedwald's formula.[15]

On the day of the recording, subjects reported to the lab about 2 hours after a light breakfast devoid of coffee or tea. Height and weight were measured and BMI was calculated as weight in kg divided by the square of the height in units of meter squared. Waist circumference and hip circumference were measured and waist-hip ratio calculated.

Cardiovascular Autonomic Function Testing

Subjects were rested in supine position for at least 10 minutes, after which resting ECG was recorded with the subjects remaining supine for another 5 minutes. During this time, subjects were instructed to relax and breathe as they normally would at a rate of about 12–16 breaths/min. BP measurements during autonomic reflex tests were made using the Colin Press-Mate 8800 (Colin Corporation Inc., Komaki-City, Japan) noninvasive BP monitor. BP was measured at the end 5 minutes of supine rest, immediately upon standing, at 2 minutes, and at the end of 5 minutes of quiet standing. ECG was also recorded continuously during 5 minutes standing. The 30:15 ratio was calculated as the ratio of the maximum RR interval around the 30th beat after standing to the minimum RR interval around the 15th beat after standing.[13,16] HR variation during timed breathing (HRVdb) was determined by asking the subject to lie down comfortably on a couch and breathe slowly and deeply at six breaths per minute. It was determined as the average of the differences between the maximum and minimum instantaneous HR during six deep-breathing cycles each lasting 10 seconds; that is, 5 seconds each for inspiration and expiration. The pressor response to sustained isometric handgrip performed using a handgrip dynamometer (INCO, Ambala, India) was measured at the end of 1 minute of sustained handgrip at one-third of maximum voluntary contraction.

Heart Rate Variability Analysis

The recommendations of the Task force report on HRV were followed.[5] Lead II ECG was acquired at a rate 1000 samples/s using the BIOPAC MP 100 data acquisition system (BIOPAC Inc., Goleta CA, USA) on to a MS-Windows® based PC with Acqkowledge software (BIOPAC Inc) version 3.8.2. Ectopics and artifacts were manually edited out. An artifact-free 256-s-long RR tachogram was extracted using the R wave detector; the stationarity of the tachogram was ascertained. The tachogram was saved in ASCII format and analyzed using the HRV analysis software version 1.1 (Biosignal Analysis group, Kupio, Finland). The RR tachogram was resampled at 2Hz, transformed by fast Fourier transformation (FFT) and the Welch's averaged periodogram method used to compute spectral powers.

The following time domain HRV indices were determined:

1. Mean RR interval;
2. Standard deviation of normal-to-normal RR intervals (SDNN), calculated after removal of ectopics and artifacts;
3. Square root of mean of the adjacent RR intervals (RMSSD);
4. HRV triangular index;

The following frequency domain indices were computed:

1. Total power was obtained by integrating the RR spectrum from 0.04 to 0.4 Hz;
2. Low frequency (LF) power was obtained by integrating the RR power spectrum from 0.04–0.15 Hz;
3. High frequency spectral power was obtained by integrating the RR power spectrum from 0.15–0.4 Hz;
4. To assess the relative contributions of LF and HF powers, LF power was normalized as follows: LF in normalized units (LFnu) = (LF / (LF + HF)) × 100;

A change in LF nu during standing was used as a surrogate of cardiovascular sympathovagal balance.[16]

Statistical Analysis

Data are presented as the means ± SD. SPSS (Version 13, SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Unpaired *t*-test or the Mann-Whitney U test was used as appropriate for statistical comparisons between the two groups. LF and HF powers were skewed and therefore log transformed and then analyzed. A 2-tailed P value <0.05 was considered statistically significant.

RESULTS

Subjects' baseline data are shown in Table 1. Subjects in the two groups were matched for age and BMI. Resting SP and DP were significantly higher in hypertensives compared to normotensive controls (P = 0.0001 for both). HDL-C was significantly lower in hypertensives compared to normotensive

Table 1. Subjects' Baseline Data

Parameter	Normotensives (n = 17)	Hypertensives (n = 35)	P Value
Age (yr)	35.5 ± 7	38.8 ± 6.8	0.11
Body mass index (Kg/m^2)	23.8 ± 2.5	24.4 ± 2.7	0.46
Waist-hip ratio	0.91 ± 0.05	0.94 ± 0.06	0.09
Systolic pressure (mmHg)	111 ± 7	155 ± 17	<0.0001
Diastolic pressure (mmHg)	71 ± 5	101 ± 8	<0.0001
Fasting blood glucose (mg/dL)	86 ± 17	89 ± 14	0.609
Total cholesterol (mg/ dL)	170 ± 28	188 ± 34	0.154
Triglycerides (mg/dL)	112 ± 44	158 ± 75	0.087
HDL-cholesterol (mg/dL)	52 ± 8	38 ± 5	0.0001*
LDL-cholesterol (mg/dL)	97 ± 28	118 ± 33	0.089
VLDL-cholesterol (mg/dL)	21 ± 7	32 ±15	0.053
HRVdb	26 ± 9	21 ± 8	0.03†
30: 15 ratio	1.43 ± 0.26	1.39 ± 0.32	0.69

Data are expressed as the means ± SD. HRVdb = heart rate variation during deep breathing test.
*P < 0.001.
†P < 0.05.

Table 2. Mean RR and Heart Rate Variability Indices during 5-Minute Supine Rest and 5-Minute Quiet Standing

Parameter	Normotensives (n = 17)		Hypertensives (n = 35)		P Value	
	Supine (1)	Standing (2)	Supine (3)	Standing (4)	Supine 1 vs. 3	Standing 2 vs. 4
Mean RR (ms)	816 ± 119	731 ± 90	809 ± 119	732 ± 107	0.85	0.97
SDNN (ms)	28 ± 20	33 ± 16	27 ± 12	28 ± 10	0.88	0.16
RR triangular index	0.07 ± 0.02	0.07 ± 0.02	0.05 ± 0.02	0.06 ± 0.02	0.02*	0.07
RMSSD (ms)	31 ± 16	21 ± 9	23 ± 14	19 ± 11	0.07	0.50
Log LF power ($ms^{2)}$	2.03 ± 0.49	2.07 ± 0.43	1.80 ± 0.38	1.82 ± 0.42	0.10	0.06
Log HF power ($ms^{2)}$	1.89 ± 0.45	1.56 ± 0.31	1.57 ± 0.49	1.37 ± 0.43	0.03*	0.07
LF in normalized units	57 ± 16	74 ± 13	62 ± 17	71 ± 13	0.33	0.49

Data are expressed as the means ± SD.
*P < 0.05.
SDNN = standard deviation of normal-to-normal RR interval; RMSSD = square root of the mean squared differences of successive RR intervals; LF = low frequency spectral power of RR intervals; HF = high frequency spectral power of RR intervals.

controls (P = 0.0001). Differences in fasting blood glucose and other lipid profile indices were statistically insignificant (P > 0.05 for all). HRVdb was significantly reduced in hypertensives (P = 0.03).

Mean RR and HRV indices during supine rest and quite standing are shown in Table 2. RR triangular index, a geometric HRV measure and HF power in absolute units were significantly lower in the supine position in hypertensives compared to normotensive controls (P < 0.05). The logarithm of LF and HF powers during supine rest were reduced in hypertensives, but only HF power showed significant differences in supine position (P = 0.1, 0.03 respectively). The percentage change in LF nu during standing was lesser in hypertensives compared to normotensives (P = 0.34). There was a 37% increase in LFnu upon standing in normotensives compared to a 26% increment in hypertensives.

BP and HR changes during quiet standing and during 1 minute sustained isometric handgrip test are shown in Table 3. Even though the maximum voluntary contraction was significantly higher in normotensives compared to hypertensive group (P = 0.04) the pressor responses to isometric handgrip were comparable in both groups. The pressor response to 5 minutes of quite standing was also comparable (P > 0.1 for all comparisons).

Table 3. Change in Blood Pressure (BP) and Heart Rate (HR) during Standing and During 1-Minute Sustained Isometric Handgrip

Parameter	Normotensives (n = 17)	Hypertensives (n = 35)	P Value
Changes in BP and HR during standing			
Systolic pressure (mm Hg)			
2 minute after standing	4 ± 8	3 ± 8	0.77
5 minutes after standing	4 ± 7	4 ± 9	0.73
Diastolic pressure (mm Hg)			
2 minutes after standing	7 ± 4	8 ± 8	0.64
5 minutes after standing	9 ± 4	8 ± 6	0.81
HR (bpm)			
2 minutes after standing	9 ± 7	8 ± 6	0.60
5 minutes after standing	9 ± 8	9 ± 7	0.90
BP and HR response to sustained isometric handgrip			
Maximum voluntary contraction (Kg)	29 ± 3	27 ± 5	0.04*
Systolic pressure (mm Hg)	11 ± 5	16 ± 9	0.07
Diastolic pressure (mm Hg)	9 ± 4	13 ± 8	0.07

Data are expressed as the means ± SD. bpm = beats per minute.
*P < 0.05.

Table 4. Spearman Correlation (r) between Classic Indices of Autonomic Function and Heart Rate Variability Indices Obtained from 5-Minute RR Tachogram in Normotensive (NT; n = 17) and Hypertensives (HT; n = 35)

		Rest					Standing				
Parameter		**SDNN**	**LF p**	**HF p**	**LF+HF p**	**LF nu**	**SDNN**	**LF p**	**HF p**	**LF+HF power**	**LF nu**
Mean RR supine	NT	0.2	0.4	0.4	0.4	0.1	0.1	0.2	0	0.2	0.3
	HT	0.6*	0.4†	0.5*	0.4*	−0.2	0.6*	0.4†	0.6*	0.5*	−0.3†
Mean RR standing	NT	0.1	0.5†	0.3	0.5	0.2	0.1	0.4	0.1	0.4	0.6*
	HT	0.4†	0.2	0.3	0.2	−0.1	0.4†	0	0.6*	0.2	−0.5*
HRV DB	NT	0.2	0.4	0.3	0.5	0.2	0.3	0.3	0.6†	0.3	−0.1
	HT	0	0	0.2	0.1	−0.4†	0	0	0.2	0.1	−0.1
30:15 ratio	NT	0.2	0.2	0.2	0.2	−0.2	0.3	0.2	0.2	0.2	0.2
	HT	0.4†	0.5*	0.3†	0.5*	0	0.4†	0.5*	0.2	0.5*	0.3
Systolic pressor response to IHG	NT	0.1	−0.1	−0.2	−0.1	0	−0.1	0.2	−0.2	0.2	0.3
	HT	0	−0.1	−0.1	−0.1	0	−0.3	−0.2	−0.1	−0.2	−0.1
Diastolic pressor response to IHG	NT	0	0.1	0.2	0.1	−0.1	−0.2	−0.3	−0.3	−0.3	−0.1
	HT	−0.1	−0.1	0	−0.1	−0.2	−0.3	−0.3	−0.2	−0.2	−0.2

*P < 0.01.
†P < 0.05.

Correlations between HRV indices during supine rest and classic indices of cardiovascular autonomic regulation are noted in Table 4; certain other interesting correlations are noted in Table 5.

A significant positive correlation between SDNN and mean RR at rest fits into the linear relationship noted between mean RR and overall HRV (both surrogates of cardiac vagal tone) by Goldberger; that is, up to a certain limit, higher the mean RR, higher the balance between vagal and sympathetic effects (called vagal-sympathetic effect) on the heart. In contrast, the strength of the same correlation is much lesser (r = 0.4) for the standing condition. Surprisingly, such a correlation is absent in normotensives both during rest and during standing.

The 30:15 ratio, an index of the latency as well as the amplitude of baroreflex regulation of HR,[17] correlates with LF power, the sum of LF and HF powers and also SDNN (r = 0.5 for each correlation) in hypertensives although such a correlation was not observed in normotensives. Surprisingly, there is a positive correlation between age and LF nu during supine rest is in hypertensives (Table 5) whereas in normotensives, this correlation coefficient is

Table 5. Spearman Correlation (r) between Age, BMI, WHR PP RPP and Heart Rate Variability Indices Obtained from 5-Minute RR Tachogram in Normotensive (NT; n = 17) and Hypertensives (HT; n = 35)

		Rest					Standing				
Parameter		**SDNN**	**LF p**	**HF p**	**LF+HF p**	**LF nu**	**SDNN**	**LF p**	**HF p**	**LF+HF p**	**LF nu**
Age	NT	−0.4	−0.3	0.1	−0.1	−0.5	−0.3	−0.4	−0.4	−0.3	−0.2
	HT	−0.2	−0.1	−0.4*	−0.3	0.5†	−0.2	−0.1	−0.2	−0.2	0
BMI	NT	−0.2	−0.1	−0.3	−0.2	0.5*	0	0	−0.3	−0.1	0.3
	HT	−0.2	−0.2	−0.1	−0.2	−0.1	−0.2	−0.3	−0.3	−0.3	−0.1
WHR	NT	−0.4	−0.4	−0.5†	−0.5*	0.3	−0.5	−0.2	−0.6*	−0.3	0.4
	HT	−0.1	0	−0.1	−0.1	0.1	−0.3	−0.3	0	−0.3	−0.3
PP	NT	0.2	0.3	0.1	0.3	0.1	0.4	0.2	0	0.2	0.4
	HT	−0.3	−0.3	−0.4*	−0.4*	0.1	−0.4*	−0.4*	−0.4*	−0.4*	0
RPP at rest	NT	0	−0.3	−0.2	−0.3	−0.4	0.1	−0.1	0.1	0	−0.2
	HT	−0.6†	−0.5†	−0.5†	−0.5†	0.2	−0.7†	−0.5†	0.7†	−0.5†	0.3

*P < 0.05.
† P < 0.01.

negative. However, there was no correlation between pressor response to isometric handgrip and any of the HRV indices during supine rest or standing in both normotensives and hypertensives.

Surprisingly, there was no correlation between HRVdb, a well-established, reliable, and reproducible marker of parasympathetic modulation of RR intervals, and other time-domain or spectral measures of HRV in hypertensives; in contrast, there was a modest positive correlation between HRVdb and HF nu (an index of parasympathetic modulation of SA node) in normotensives.

DISCUSSION

In the present study, we planned to evaluate short-term HRV in patients newly diagnosed to have hypertension and not having taken antihypertensive medication in the past. It can be seen that whereas mean RR interval is comparable in hypertensives and normotensives, indices of RR variability viz. RMSSD, RR triangular index are significantly reduced in hypertensives; further, HR variation during timed deep breathing, a readily measured classic autonomic index, is clearly attenuated in new-onset hypertension. During resting conditions, SDNN reflects all components responsible for HRV, and presumably, most HRV is vagally mediated under these conditions. RMSSD has been suggested to reflect vagal contributions to HRV occurring at respiratory frequency.[18] Thus, the study of beat-beat changes in RR intervals has indeed afforded considerable insight into the autonomic modulation of the heart by the two limbs of the autonomic nervous system.[19]

The HR response to timed deep breathing (HRVdb) is a classic test of parasympathetic modulation of RR intervals and its reproducibility has been previously established; furthermore, the response is abolished by atropine.[13] The fact that HRVdb is reduced in new-onset hypertensives is thus clear evidence of diminished vagal modulation of RR intervals in this group.

The magnitude of HF power, which is an index of vagally mediated respiration-related sinus arrhythmia[5] because it occurs at the frequency of respiration and is abolished by atropine, was significantly lower in hypertensives compared to controls at least during supine rest; however, both hypertensives and normotensives showed a comparable attenuation of HF powers during standing ($P = 0.12$, Mann-Whitney U test) suggesting that sympathetic attenuation of respiratory sinus arrhythmia is comparable in the two groups during quiet standing. In contrast, the interpretation of the absolute value of LF power is slightly more complex because RR interval oscillations at this frequency are mediated by changes in both vagal and sympathetic outflows to the heart;[19,20] these LF oscillations might reflect baroreflex mediated changes in RR interval or feedforward oscillations of RR interval leading to BP oscillations.[19,20] There is a trend toward lower LF powers in hypertensives at least for the standing position ($P = 0.06$) and this possibly contributes to diminished overall HRV. One physiologic interpretation of diminished overall HRV is an increase in the balance of sympathetic and vagal effects on the SA node. There is evidence that changes in LF nu during sympathoexcitatory states furnish an index of a change in sympathovagal balance and differences in LF nu at baseline were insignificant. In line with earlier observations made by Huikuri et al.,[21] we also found that the percentage increment in LF nu on standing in hypertensives (26%) is much lesser compared to normotensives (37%) although the difference is not statistically significant ($P = 0.34$). Our results are in line with studies in which short-term HRV has been noted to be diminished in hypertensives.[5–9]

Our finding of an enhanced pressor response to isometric handgrip in hypertensives suggests that pressor reactivity is heightened in hypertensives. This observation is probably stressor specific. Murakami et al.[22] have reported exaggerated pressor responses in hypertensives to isometric handgrip, bicycle ergometer exercise, and mental arithmetic.

The present study provides clear evidence that short-term HRV is reduced in middle-aged hypertensive men with new-onset hypertension. This indicates that there is diminished short-term autonomic modulation of RR intervals in hypertensives, and this likely reflects an increase in cardiovascular sympathovagal balance; by this is meant an increase in the balance of sympathetic versus vagal effects on the cardiovascular system. It must indeed be emphasized that HRV does not quantify autonomic nerve activity and that RR modulation is influenced by responsiveness of the effectors; that is, the heart and the vasculature to autonomic nerve traffic. Finally, the presence of significant correlations between time domain and spectral indices of HRV and the classic autonomic indices only lends credibility to the physiologic interpretation placed upon both of them.

A recent study by Lucini et al.[23] has demonstrated evidence of autonomic dysregulation even in patients with high-normal resting BP. However, the prognostic value of reduced short-term HRV in hypertensives needs to be investigated in future studies. Furthermore, the effect of various classes of antihypertensive drugs on short-term HRV and its relation to BP control is also an interesting and important issue that needs to be well researched in future studies.

Acknowledgment: *The authors wish to thank the Biomedical Signal Analysis group, Department of Applied Physics, University of Kuopio, Finland, for providing the HRV analysis software version 1.1. The software is distributed free of charge upon request from this website: http://venda.uku.fi/research/biosignal. The authors thank their colleague Dr. Prakash ES for useful comments and for correcting a draft version of this manuscript.*

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