HEART RATE VARIABILITY IN NORMOTENSIVE SUBJECTS WITH FAMILY HISTORY OF HYPERTENSION

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Abstract: Hypertension (HT) is a major silent disease affecting young people because of their hereditary and modern lifestyles. Target organ damages occur before overt hypertension is diagnosed. Many offspring of HT parents show early changes in their cardiovascular autonomic functions. Heart rate variability (HRV) provides a window to understand the cardiac autonomic balance. This study was designed to quantify and to compare the HRV among the normotensive young male offspring without history of parenteral hypertension & diabetic (control group, n=25, age 20.8±2.4, BMI 24.4±3.1) with parenteral history of hypertension & non diabetic (study group n=25, age 19.7±1.9, 24.05±3.5). Blood pressure, heart rate (HR), indices of short term HRV during supine rest and quiet standing, HR variation during timed controlled deep breathing was compared between the two groups. There were significant difference in low frequency (LF) power, HF power, total power. LF and HF expressed also in normalized units at rest and standing. In time domain standard deviation of normal to normal RR interval (SDNN) at supine rest and standing were significant. Respiratory sinus arrhythmia (RSA), HF in normalized units, deep breathing difference (BDD) and the ratio of maximum RR to minimum RR were also significant in the control group than study group. In the present study there was an increased sympathetic and decreased parasympathetic activity in subjects with parenteral history of hypertension.

Key words: heart rate variability sympathovagal balance autonomic nervous system

INTRODUCTION

There is a clear evidence that autonomic dysregulation underlies the initiation and maintenance of hypertension (1). The arterial baroreflex mechanism senses and regulates blood pressure through effects on the heart, blood vessels, renal excretion of
sodium and water (2). Normotensive subjects with family history of hypertension show greater sympathetic nervous system activity and also early parasympathetic attenuation. Pressor response to mental arrhythmia are significantly greater in hypertension. HRV in simple is the quantitative measure of heart rate fluctuations around the mean heart rate. It is a valuable research tool to study and to investigate sympathetic and parasympathetic function of the cardiac autonomic system (3, 4). HRV seems to be diminished in many studies among the subjects of recent onset hypertension (5). It has been known that baroreflex had little to do with long term BP regulation (6). However recently the role of neural regulation in long term BP control is also gaining importance (7, 8). At present spectral analysis of beat to beat cardiovascular variability has been a novel method in the assessment of risk in primary hypertension (9, 10). At presently HRV investigation has superseded classic test for autonomic function because it (HRV) quantifies sympathetic and parasympathetic activity (11–13). On the other hand the classic autonomic function testing can be readily performed in a clinical settings using simple, inexpensive equipment. They are very well based on the assumption that BP response are mediated by the sympathetic nervous system the HR response are, for the most part, vagally mediated (14–16). In the last few decades, investigators have recognized the importance of the relationship between autonomic system and cardiovascular mortality. Among the primary hypertension nearly 30% has genetic predisposition. There are very many number of genes responsible for the development of primary HT. In the recent years few candidate genes have been identified for primary hypertension (27).

In the present study, we tested the hypothesis that normotensive young male adults, with parental history of hypertension without the history of diabetic show a difference in the cardiovascular autonomic function at rest, standing and timed deep breathing. Moreover a short term HRV indices may give a valuable information about the cardiovascular autonomic function in young subjects.

MATERIAL AND METHODS

The Ethical committee of Stanley Medical College Chennai, India, approved this study protocol. A total of fifty male subjects were inducted for the study from 1st year to final year MBBS of Stanley Medical College Chennai. History of primary hypertension was determined from the parents of the offspring to be studied. A detail information regarding, dosage and duration and type of antihypertensive therapy were carefully recorded from the parents. Diabetics status of the parents were ruled out by WHO protocol 2003. Then the subjects (offspring) for the study were classified in to the following two groups, each group consisting of 25 men only.

Control group: Normotensive subjects whose parents are neither Hypertensive nor diabetic (25 subjects)

Study group: Normotensive subjects whose parents are Hypertensive on treatment but not diabetic (25 subjects)

Inclusion Criteria (common to both study and control groups)

Healthy males in the age group of 18–26
Then the subjects were asked to stand spontaneously on the ground for 10 min. ECG lead II was also recorded on spontaneous standing. Controlled deep breathing was recorded after giving proper instruction and sufficient training. The subjects were made to lie down comfortably on a couch with slight headup and through verbal signal they were asked to breathe slowly and deeply at the rate of 6 respiratory cycles/min in such way that inspiration last 5 sec and expiration last 5 sec per respiratory cycle. An event marker was inserted on the recording screen of ECG, at the start of giving verbal commands. The average RR intervals during inspiration and expiration were calculated for each respiratory cycle for the period controlled deep breathing which last for 1 minute. This average RR interval multiplied by sixty seconds (1 minute) gives the heart rate during each phase of respiratory cycle. The maximum HR during the inspiration minus the minimum heart rate during expiration gives the deep breathing difference (DBD). Also HF in normalized units of HRV was taken for analysis during the 1 minute of controlled deep breathing in between two groups.

Heart rate variability analysis

The recommendations of Task Force on HRV were followed (12). An RR series was extracted from ECG using maximum amplitude & sharpness of the peaks for R wave detection, these are RMS proprietary algorithms & validated with Fluke Biomedical, USA. After exclusion of artifacts and ectopics a stationary 256s RR series was chosen and analysed with Finland v1.1 software for HRV (Bio-signal analysis Group, Finland). Mean RR was measured in
milliseconds. In the time domain, the standard deviation of normal to normal RR intervals (SDNN) was taken as an index of overall HRV. The RR series was resampled at 4 Hz, its mean and trend removed, a Hann window applied and the 1024 data-point series transformed by Fast Fourier transformation. Low Frequency (LF) and High Frequency (HF) spectral powers were determined by integrating the power spectrum between 0.04 and 0.15 Hz and between 0.15 and 0.4 Hz, respectively. The sum of LF and HF powers were also calculated (12). Spectral powers were expressed in absolute units of msec\(^2\). Low and high frequency power were expressed in normalized units.

**Statistical analysis**

The data were examined for normality. Wherever the data was not normally distributed, nonparametric test was used. Data expressed as mean±SD. Changes in parameters within the group during the various manoeuvres were analysed using student’s paired t-test for normally distributed data and Mann-Whitney U-test for skewed data. Comparisons between the four variables were analysed using one-way analysis of variance (ANOVA). A correlation between normally distributed indices were determined using the Pearson correlation coefficient. The null hypothesis was rejected at P<0.05, SPSS version 11 and Microsoft Excel were used for analysis of data.

**RESULTS**

There were no significant differences in the age, BMI and physical index in between the two groups (Table I). There were no significant differences in the basal systolic and diastolic blood pressure, in between the two groups. There was an increase in the resting HR in the study group compared to control group which was not very significant (Table I). Higher LF power values is seen in study group at supine rest. There was a decrease HF power seen in the study group at supine rest. Total power was decreased in the study group at supine position. LF normalized units (nu) was higher in the study group at supine rest HF nu was reduced in the study group at supine rest (Table II).

**TABLE I:** General parameters, Basagl heart rate (BHR), Blood pressure during supine rest and Heart rate variation during deep breathing.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=25)</th>
<th>Study group (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>19.7±1.9</td>
<td>20.8±2.4</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI in kg/m(^2)</td>
<td>24.4±3.1</td>
<td>24.05±3.5</td>
<td>0.71</td>
</tr>
<tr>
<td>HR in b.p.m</td>
<td>68.6±10.4</td>
<td>74.9±11.0</td>
<td>0.05</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>103.1±7.0</td>
<td>106.4±8.9</td>
<td>0.15</td>
</tr>
<tr>
<td>DBP mm Hg</td>
<td>65.7±7.2</td>
<td>69.8±7.8</td>
<td>0.06</td>
</tr>
<tr>
<td>PP mm Hg</td>
<td>37.2±7.7</td>
<td>38.2±8.2</td>
<td>0.66</td>
</tr>
<tr>
<td>HRV (DBD)</td>
<td>22±9</td>
<td>16±6</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

Student independent t-test. Data are the mean±SD, P<0.05, P<0.001 compared with both groups. BP: Blood pressure; BMI: body mass index; HR: heart rate; SBP, DBP: systolic and diastolic BP respectively; PP, pulse pressure; HRV (DBD), heart rate variation during deep breathing.

On standing there was an increase in the heart rate among both groups. This was more significant in the control group. LF power was significantly increased in the study group. HF power was decreased in the study group. LF nu increased and HF nu decreased during standing in study group. SDNN was significantly decreased in the study group during standing (Table II) and there was
decrease in the total variability in the study group.

During the controlled deep breathing the deep breathing difference (DBD) was significantly low in the study group compared to control group. HF in power was significantly reduced in the study group compared control group. Among the several correlations tested, the following are of worth to note (i) a statistically significant negative correlation between mean RR and HF power in both groups during supine rest (ii) a significant inverse correlation between LF in normalized units and mean RR during standing (Table III).

TABLE II: Mean RR and heart rate variability indices during supine rest and standing in the two groups (P values for comparisons of parameters are given below) (n=25 in each group).

<table>
<thead>
<tr>
<th>Group</th>
<th>Supine (Control)</th>
<th>Standing (Control)</th>
<th>Supine (study)</th>
<th>Standing (study)</th>
<th>P value</th>
<th>F/dF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RR (msec²)</td>
<td>881.9± 12.5</td>
<td>707.7± 89*###</td>
<td>750.5± 22###</td>
<td>737± 15###</td>
<td>&lt;0.001</td>
<td>18.63/3.96</td>
</tr>
<tr>
<td>SDNN (msec)</td>
<td>52.2± 8.7</td>
<td>43.4± 16</td>
<td>45.2± 27</td>
<td>35.5± 17###</td>
<td>&lt;0.01</td>
<td>3.56/3.96</td>
</tr>
<tr>
<td>LF power (msec²)</td>
<td>597± 49</td>
<td>601± 415</td>
<td>363± 235</td>
<td>433± 349</td>
<td>0.35</td>
<td>18.63/3.96</td>
</tr>
<tr>
<td>HF power (msec²)</td>
<td>506± 419</td>
<td>194± 240*###</td>
<td>398± 387</td>
<td>184± 170*###</td>
<td>0.001</td>
<td>6.08/3.96</td>
</tr>
<tr>
<td>LF+HF power (msec²)</td>
<td>986± 20</td>
<td>676± 48*###</td>
<td>870± 108</td>
<td>629± 50*###</td>
<td>&lt;0.001</td>
<td>8.81/3.96</td>
</tr>
<tr>
<td>LF in nu</td>
<td>32.4± 10</td>
<td>72.7± 127</td>
<td>44.8± 79</td>
<td>73.7± 12</td>
<td>0.14</td>
<td>1.88/3.96</td>
</tr>
<tr>
<td>HF in nu</td>
<td>55.19± 15.44</td>
<td>27.29± 12.79</td>
<td>44.42± 17.41</td>
<td>41.73± 57.4**</td>
<td>&lt;0.02</td>
<td>3.32/3.96</td>
</tr>
</tbody>
</table>

Values are mean±SD; Mean RR: mean-RR intervals, SDNN: standard deviation of the averages of NN intervals, LF power, HF power, LFnu: normalized low frequency component; HF: normalized high frequency component; LF+HF power, in all 5 min segments of supine rest and standing recording. The star mark (*) depicts comparison with supine (control) subjects with standing (control), supine (study) and standing (study). The analysis of data was done by oneway ANOVA and post-hoc by Bonferroni t-test. *P<0.05; **P<0.01; ***P<0.001.

TABLE III: Correlation between mean RR with HRV for study and control during rest and standing.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>During rest</th>
<th>During standing</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>Control (n=25)</td>
<td>Study group (n=25)</td>
</tr>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>LF power</td>
<td>0.60</td>
<td>0.01</td>
</tr>
<tr>
<td>HF power</td>
<td>0.64</td>
<td>0.01</td>
</tr>
<tr>
<td>LF+HF</td>
<td>-0.15</td>
<td>0.36</td>
</tr>
<tr>
<td>LF in nu</td>
<td>-0.15</td>
<td>0.36</td>
</tr>
<tr>
<td>HF in nu</td>
<td>-0.43</td>
<td>0.04</td>
</tr>
</tbody>
</table>

P<0.005 was considered significant.

DISCUSSION

In our study we found the basal systolic and diastolic pressure were not significantly higher between the two groups. This shows the groups are normotensive at rest. Julis
et al studies had shown that those with parental history of hypertension their offspring show higher diastolic pressure probably due to hyperactive sympathetic nervous system (SNS). As a result increased SNS activity cause an increase in the heart rate, peripheral vasoconstriction resulting in the increased peripheral vascular resistance with rise in the systemic blood pressure. Mean RR did not differ at supine rest. In our study, we did not find a significant difference in the basal heart rate between the two groups. This may be due to the younger age group and the BMI was within normal limits and so almost all of them had a normal resting heart rate. Larger sample size might have shown some significant difference in the resting heart rate between the two groups. In the present study LF power was significantly increased compared to the control group even at supine rest. LF expressed in powers includes more sympathetic and less parasympathetic influence (12). LF reflects the sympathetic activity when represented in the normalized by some other workers. Further LF component of power spectral analysis is predictive of the development of hypertension in men in their later ages. Framingham study has shown adiposity to be a strong predictor of hypertension in men and women (17). It is worth to note that LF component of HRV to be a strong predictor of future hypertension though BMI, a measure of obesity. Increased in LF power was observed in the recent onset hypertension (18). LF nu was increased in study group compared to control group which indicates increased sympathetic activity.

Our results which agree with those earlier studies indicating that HF power is significantly diminished in the study group during supine rest. HF in power is the direct representation of vagal tone. Vagal tone is an important determinant of cardiovascular health. Vagal tone of an individual has insightful influence on the heart rate, cardiac output and blood pressure. Persons with poor vagal tone are more prone to develop cardiovascular diseases such as myocardial infarction, hypertension and heart failure. The amount of contribution of HF power to the total power is almost two third and so any reduction in the HF power and HF in normalized units indicate decreased vagal activity. In the present study HF in power and HFnu units are significantly decreased in the study group compared to control group. Thus our study indicates early cardiovascular vagal tone changes in the study group.

SDNN represent long term vagal modulation of cardiac functions. This may be better quantified with 24 hour ECG recording (Holter monitoring). This is because HRV is not a stationary process, i.e., a process in which the mean and variance are independent of record length. A lower SDNN indicate diminished baroreflex modulation of RR intervals. Though there was no significant reduction in the SDNN values during supine rest in the study group, but it was significantly reduced during standing. Low SDNN and low HF power, taken together, which are seen in the study group is indicative of poor vagal control in the cardiovascular system. Hence from supine rest to standing there was a significant decrease in the overall HRV in the study group compared to control group.

There are very many suggestions to
quantify sympathetic-vagal balance (SVB) in autonomic function. Many studies concur that LF/HF ratio can be used as an indicator of sympathetic-vagal balance (18). The reciprocal relationship between LF and HF is a better measurement of sympathetic-vagal balance (20). LF/HF ratio does not predict non-existence of SVB. There are differences in the opinion of SVB. On the other hand, some investigators in the field have opposing views regarding sympathetic-vagal balance. That the calculations of sympathetic-vagal balance (ratio of LF to HF) may obscure rather than illuminate human physiology and pathophysiology (21, 24). Such opposing views indicate fundamentally different approaches to LF/HF ratio, in the event of varied opinions regarding SVB by using LF/HF ratio, we did not make the variable in our study. Thus an increase LF/HF ratio along with a reduced total power indicates poor cardiovascular status of the subjects. We could not come across the above facts in our study.

Heart rate variation during deep breathing

Controlled deep breathing in an exaggeration of normal sinus arrhythmia otherwise called as respiratory sinus arrhythmias (RSA). There are very many mechanisms attributed to the changes in the heart rate during RSA. These changes in the heart rate are due to the generation of impulses by the combination of respiration-induced physical and biochemical changes. During inspiration the impulses from the lung stretch receptors produce vagal inhibition. Then the increased venous return during inspiration, due to the fall in intrathoracic pressure cause stimulation of arterial stretch receptors, which produce vagal inhibition. Moreover, the spill over of impulses from the respiratory centre in to the adjacent vagal motor neurones causes their inhibition to tachycardia. HFnu is generally taken as quantifying variable for respiratory sinus arrhythmias (18). HRV during deep controlled (HRV DB) breathing for one minute is a major reliable and reproducible marker of parasympathetic modulation of cardiac function (22). Reduced HRV DB in our study group clearly indicates that cardiac vagal effects (ie vagal modulation of RR intervals) were diminished. This may possibly be due to diminished baroreflex sensitivity (18). Deep breathing difference (DBD) in the controlled deep breathing in another important parameter for parasympathetic function. DBD is significantly reduced in the study group denoting there is an early reduction in the vagal function. Stolarz K has done a similar study showing that sympathetic activity was increased even before the hypertension developed but they could not get much changes in the parasympathetic function. The present study clearly indicates profound reduction in vagal activity in the study group in comparison with the control group during timed deep breathing.

Implications of results

The presence of significant correlation between the results of simple reflex test and spectral measures even in short term HRV supports the effortless approach for assessment of cardiac autonomic function even in normotensive subjects. The presence of significant correlation between HR response to timed deep breathing, SDNN, HFnu and total power, in the study group corroborate the use of this simple index for
assessing vagal modulation of HR in this subset. In fact the HR response to deep breathing has been shown to predict mortality following myocardial infarction (22, 23, 25). Further 24 hrs HRV recording will demonstrate the prediction of risk of arrhythmias, sudden death following a myocardial infarction and cardiovascular autonomic status in the normotensive hypertensive subjects.

Conclusion

In conclusion, we have obtained clear evidence that HRV is reduced in normotensive young men with history of parental hypertension. This lower HRV is associated with greater risk for developing latent hypertension. Estimation of LF using spectral analysis even in short term ECG recording improves the prediction of risk of developing hypertension. These findings nearly suggest that the hypothesis of autonomic dysregulation is present at an early stages of normotension. Further our study suggests that the tendency for developing hypertension sets in at an early age. It is not only enough to record blood pressure alone but also to investigate HRV analysis to find out the underlying autonomic physiology.

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REFERENCES


