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Original Article

Reliability and Effect of Submaximal Aerobic Exercise Test to Assess Cardiac Autonomic Response in Female Normotensive Offspring of Hypertensive Parents

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Abstract

Background : In recent past researches have shown genetic inheritance is an important predisposing factor for future development of hypertension in normotensive offspring of hypertensive parents (NOHP). Heightened cardiacautonomic reactivity to mental and physical stress has been reported in these population in recent past. Exercise is a physiological stressor commonly used to elicit occult cardiovascular abnormalities that are not detected at rest**.** Compare to maximal, supramaximal and high intensity chronic exercise, single bout of submaximal aerobic exercise that can also potentially evoke cardiac autonomic response even at delayed phase of recovery state has been given little attention till date. There is also paucity of data regarding effect of aerobic exercise test particularly on young female NOHP at recovery period.

Objective: The aim of this study was to evaluate the reliability and effect of single bout of submaximal aerobic exercise test to assess the cardiac autonomic response in young female NOHP.

Materials And Method: An observation and cross-sectional study was conducted at autonomic function research laboratory of Physiology department at R G Kar Medical College, Kolkata between March 2016 and February 2017 on 50 young healthy female subjects aged 18-25 years and divided them in two groups: normotensive offspring of hypertensive (NOHP) and normotensive offspring of normotensive parents (NONP) in 1:1 ratio. Resting blood pressure (BP) was recorded first manually. After that short-term heart rate

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variability (HRV) test for five minutes conducted by a multiple-channel Polyrite-D instrument for five minutes in supine position at rest and last five minutes of 15 minutes recovery phase after a single bout of submaximal (50% VO_{2max}) aerobic exercise using treadmill machine and following modified Black-Bruce protocol as well as Astrand-Rhyming nomogram. Data was analysed in frequency domains of HRV using spectral components like heart rate [HR], low frequency at normalised unit [LFnu], high frequency at normalised unit [HFnu], LF/HF ratio and total power [TP].

Results: Spectral components of HRV had shown exaggerated sympathetic excitation (mean $LFnu_{basal}$: 57.14±12.313, mean $LFnu_{recovery}$: 66.403±12.471, p value: 0.0012, t value: 3.686), attenuated parasympathetic modulation (mean $HFnu_{basal}$: 42.839±12.217, mean $HFnu_{recovery}$: 32.224±12.335, p value: <0.0001, t value: 5.585) and overall sympathovagal imbalance (SVI) (mean LF/HF_{basal}: 1.559±0.858, mean $LF/HF_{recovery}$: 2.378±0.925, p value: <0.0001, t value: 5.788) in NOHP only at recovery phase but not in NONP. Moreover, post exercise frequency domain HRV analysis had shown significant difference between the two groups, higher mean values of LFnu, LF/HF ratio and lower HFnu as well as attenuated TP were observed among NOHP compared to NONP.

Conclusion: Study indicated that exercise at 50% of VO_{2max} was reliable to implement a sub-maximal load to evoke substantial cardiac autonomic response and apparently healthy young female NOHP exhibit impaired autonomic modulation which could lead to develop hypertension in future.

Introduction

Essential hypertension (HTN) is a common multifactorial (polygenic) disorder that involves complex genetic, vasoconstrictive, environmental and other risk factors (1). An increased prevalence of hypertension is seen in South Asia due to industrialization, lifestyle and behavioural change and rapid strengthening in economic sector (2).

Many studies in recent past observed hereditary nature of essential hypertension. Researchers had shown that 25% of children with one hypertensive parent and 50% of children with two hypertensive parents will eventually become hypertensive (3, 4). The above evidences emphasized the need to explore the family history of hypertension even in a normotensive individual. Till date, few studies were conducted to understand the nature of cardiac autonomic activity by using minimal stressor that causes the young female normotensive offspring of hypertensive parents (NOHP) to enter a stage of pre-hypertension or hypertension (5, 6). Spectral analysis in frequency domain of heart rate variability (HRV) has been recently used as sensitive tool for assessment of autonomic dysfunctions in various clinical disorders including assessment of risk in primary hypertension at an early age (7, 8) as well as an important index that can be used to quantify parasympathetic reactivation after exercise (9). On the other hand, under physiological circumstances exercise is a stressor which can be helpful to evaluate cardiac autonomic dysregulation that are commonly not detected at basal state (10, 11). Submaximal aerobic exercise protocol helps to overcome many of the limitations of maximal exercise testing (12). This stress test can be used to predict VO_{2max}, to make diagnoses and assess functional limitations, to assess the outcome of interventions such as exercise programs, to measure the effects of pharmacological agents and also to examine the effect of recovery strategies on exercise performance (13-17). Compare to maximal, supramaximal and high intensity chronic exercise, single bout of submaximal aerobic exercise that can also potentially alter cardiac autonomic reactivity even at recovery phase in apparently healthy female NOHP has been given little attention till date (18).

Objective

The aim of this study was to evaluate the reliability and effect of single bout of submaximal aerobic exercise test to assess the cardiac autonomic response in young female normotensive offspring of hypertensive parents (NOHP).

Methods

An observation and cross-sectional study was conducted on 50 healthy female subjects with and without parental history of hypertension [1:1 ratio] at autonomic function research laboratory of Physiology department at R G Kar Medical College, Kolkata between March 2016 and February 2017 after getting proper ethical clearance from the Ethics Committee of R G Kar Medical College, Kolkata. Subjects with parental history of hypertension was labelled as NOHP [n=25] and rest of them without parental history of hypertension was named as NONP [n=25]. Inclusion criteria for the present study were:

1. Young healthy normotensive female medical, paramedical and nursing students (age group: 18-25 years) of this institution with and without parental history of hypertension. Positive family history of hypertension was defined as one or both parents is/are getting treatment for hypertension ((BP above 150/90 mm of Hg as per JNC 8 guidelines) (19) for at least 2 years as confirmed from personal medical record of the individual. Negative family history of hypertension was defined as the absence of any evidence of hypertension in both parents and by measurement of parents' BP (measurements on two different occasions in triplicate at 2-min intervals).

2. Cases were selected from offspring of only single hypertensive parent (either mother/father).

3. All subjects had regular menstrual cycle as determined by menstrual assessment charts completed for 3 consecutive months before participation. This age group had been chosen because in entire adulthood this age has the lowest incidence of any kind of cardiovascular diseases (20).

4. All study subjects were non-smoker, non-alcoholic and had systolic blood pressure (SBP) & diastolic blood pressure (DBP) were ≤150 mm of Hg & ≤ 90 mm of Hg respectively.

Whereas exclusion criteria were:

1. Smokers, addicts & any drug intake on a regular basis that affects autonomic nervous system.

2. Students with known personal history of Hypertension, Cardiovascular Diseases, Endocrine and Autoimmune-Diseases.

3. Family history of Diabetes, Coronary artery diseases.

4. Any acute illness, recent illness during the past three weeks or so.

5. Subjects having history of ongoing menstruation on the day HRV examination.

6. Subjects having history of hypertension of both parents.

The study was conducted in departmental laboratory between 9.00 AM and 10:30 AM. A written consent had taken from each of the participant before starting the test and a lady attendant was there all the time while doing the procedure. At the beginning all the subjects were explained in detail about the testing procedure. Experiments were done in a quiet room during which subjects lay supine, awake and breathing normally. After measuring height, weight waist and hip circumference, subjects were given a 30 minutes mandatory rest period. At the end of 30 minutes rest period, blood Pressure (BP) were recording manually by aneroid sphygmomanometeron two different occasions on triplicate at 2-min intervals. Least baseline BP were determined and noted in the case sheet. Thereafter short term HRV test was conducted by a multiple-channel Polyrite-D instrument for five minutes in supine position. All

the subjects were performed single bout (one episode only) of sub-maximal aerobic exercise on a treadmill machine following modified Black-Bruce protocol (Fig. 1) (21, 22) till the pulse rate (PR) achieved 138 beats/ minute by them which was monitored by pulse-oximeter. According to Astrand and Ryhming nomogram estimated maximum oxygen consumption (VO_{2max}) can be determined by reading horizontally from the body weight scale (step test) or workload scale (cycle test / motorized treadmill test) to the oxygen uptake (VO_2) scale (figure 2) where it was mentioned that sub-maximal workload (50% of VO_{2max}) could be achieved by reaching this pulse rate (12, 23).

Stage	Speed (mph)	Grade (%)	Duration (min)
0	1.7	0	3
0.5	1.7	5	3
1	1.7	10	3
2	2.5	12	3
3	3.4	14	3
4	4.2	16	3
5	5.0	18	3
6	5.5	20	3
7	6.0	22	3

Fig. 1 : Modified Black-Bruce protocol for treadmill test) (15, 16).

The exercise was continued for next five minutes carrying the same workload before terminating the procedure. After that subject was allowed to take rest in supine position and finally post exercise HRV

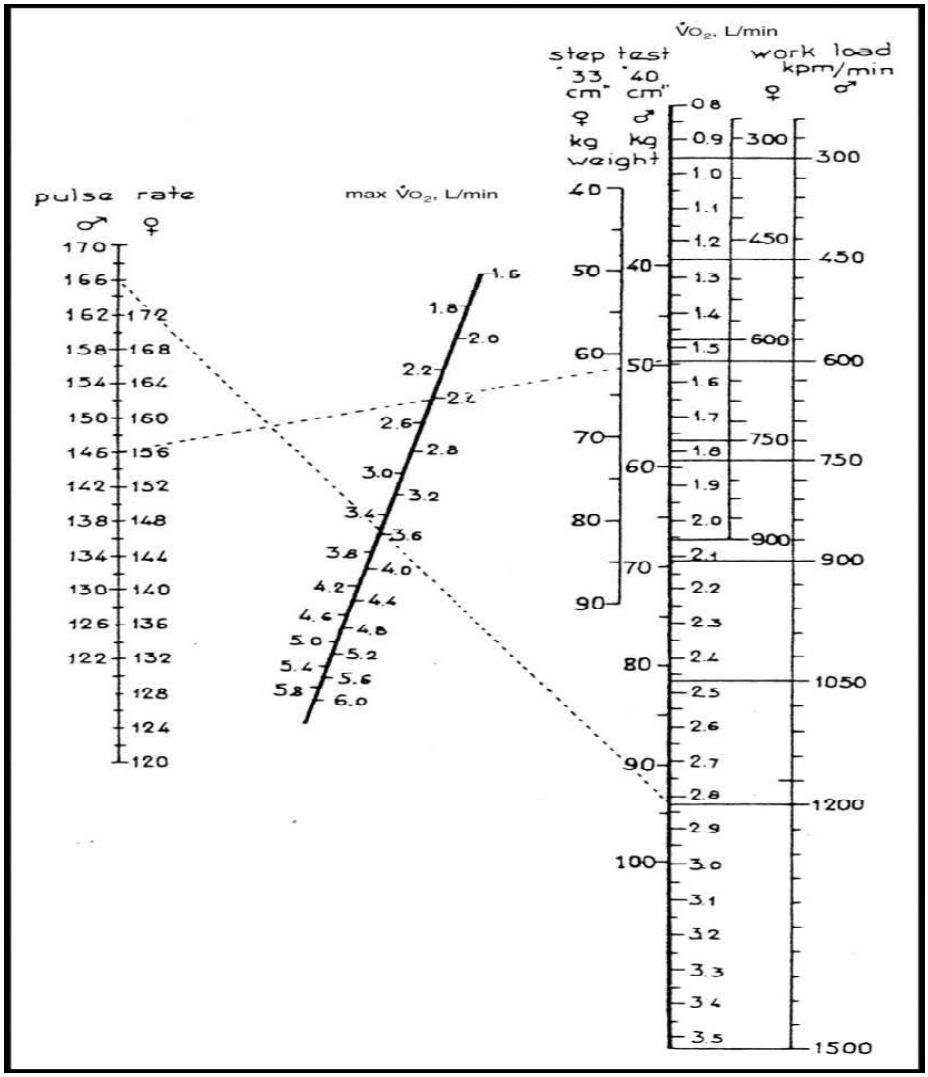

Fig. 2: Astrand-Rhyming nomogram.

was recorded again during the last five minutes of 15 minutes recovery phase.

Statistical analysis

Data thus obtained was analyzed with appropriate statistical methods. At first mean and standard deviation (SD) was calculated using Microsoft Excel Sheet (Windows 7) & expressed as Mean±SD. Paired t test was used for pre and post exercise variable data analysis among subjects by using Graphpad Quickcalc Software, California USA. Statistical significance was assigned at $P<0.05$.

Results

Table I had shown all study subjects were young and BMI, waist-hip ratio, SBP and DBP were having within normal range.

Table IIa had shown exaggerated sympathetic excitation [LF_{nu}], attenuated parasympathetic modulation [HF_{nu}] and overall sympathovagal imbalance (SVI) [LF/HF ratio] among NOHP in spectral components of HRV. There was no significant difference for heart rate and total power.

Table IIb had shown there was no significant difference between pre and post exercise values of study variables.

Table IIIa had shown that at rest:

1. Mean values of RHR was significantly higher among NOHP compared to NONP.

2. All other study variables had no significant difference between the groups.

Table IIIb had shown:

The mean values of HRR, LF_{nu}, LF/HF ratio were significantly higher but mean values HF_{nu} and total power were lower among NOHP compared to NONP subjects at post exercise recovery state.

TABLE I: Anthropometric variables of the study population (n=50).

Variables	*Measured values*
AGE (years) (Mean±SD)	19.36±0.851
BMI (kg/m^2) (Mean±SD)	22.434±3.427
WAIST-HIP RATIO (Mean±SD)	0.847±0.045
SBP (Mean±SD)	113.16±14.507
DBP (Mean±SD)	74.8±2.984

Discussion

In our study we had chosen fixed intensities targeting percentage of VO_{2max} for all the participants throughout

TABLE IIa: Comparison of spectral components of HRV between resting state and recovery phase among NOHP.

HRV indices	*Resting phase*	*Recovery phase*	*t value*	*p value*
Heart Rate (beats/min) (Mean±SD)	88.64±11.546	90.0±8.892	0.807	0.427
LF_{nu} (Mean±SD)	57.14±12.313	66.403±12.471	3.686	0.0012*
HF_{nu} (Mean±SD)	42.839±12.217	32.224±12.335	5.585	<0.0001*
LF/HF (Mean±SD)	1.559±0.858	2.378±0.925	5.788	<0.0001*
Total power (ms^2) (Mean±SD)	595.479±527.694	372.843±270.866	1.844	0.077

TABLE IIb: Comparison of spectral components of HRV between resting state and recovery phase among NONP.

HRV indices	*Resting phase*	*Recovery phase*	*t value*	*p value*
Heart rate (beats/min) (Mean±SD)	79.72±8.619	81.48±9.265	1.937	0.064
LF_{nu} (Mean±SD)	51.742±14.974	54.936±17.601	1.213	0.236
HF_{nu} (Mean±SD)	48.217±15.007	45.108±17.649	1.187	0.246
LF/HF (Mean±SD)	1.353±0.975	1.564±0.995	1.274	0.214
Total power (ms^2) (Mean±SD)	776.886±747.772	638.073±548.138	0.954	0.349

TABLE IIIa : Comparison of different study parameters between NOHP and NONP at rest.

Variables	*NOHP [n=25]*	*NONP [n=25]*	*t value*	*p value*
Resting heart rate (RHR) (beats/min)(Mean±SD)	88.64±11.546	79.72±8.619	3.095	0.003*
LF_{nu} (Mean ±SD)	57.140±12.313	51.742±14.974	1.392	0.170
HF_{nu} (Mean ±SD)	42.839±12.217	48.217±15.007	1.389	0.171
LF/HF ratio (Mean±SD)	1.559±0.858	1.353±0.975	0.793	0.431
Total power (ms^2) (Mean±SD)	595.479±527.694	776.886±747.772	0.991	0.326

TABLE IIIb : Comparison of different HRV indices between NOHP and NONP at recovery period.

Variables	*NOHP [n=25]*	*NONP [n=25]*	*t value*	*p value*
Heart rate recovery (HRR) (beats/min) (Mean±SD)	90.0±8.892	81.48±9.265	3.317	0.001*
LF_{nu} (Mean±SD)	66.403±12.471	54.936±17.601	2.657	0.010*
HF_{nu} (Mean±SD)	32.224±12.335	45.108±17.649	2.991	0.004*
LF/HF (Mean±SD)	2.378±0.925	1.564±0.995	2.995	0.004*
Total power (ms^2) (Mean±SD)	372.843±270.866	638.073±548.138	2.169	0.035*

the testing condition forming homogenous groups for power values. As there are no “gold standards” for training load prescription till date (9), although this exercise test could be helpful because researchers had shown a steady-state heart rate can be obtained for each workload and there is a linear relationship between heart rate and work load for everyone (24). The two modalities commonly used in aerobic exercise are treadmill and cycle ergometry. In this present study treadmill machine was used for exercise stress test as it appeared to be the most widely used modality due to familiarity with upright locomotion and greater voluntary muscle activation, cycling protocols present an opportunity to test individuals with coordination or orthopedic limitations. Furthermore, opting to use a cycle ergometer over treadmill might be resulted in a more quantifiable workload (Watts) whereas treadmill was provided an opportunity to use a progressive ramp protocol allowing for more reproducible outcomes (25). However, VO_{2max} attained using treadmill protocols tend to produce up to 20% greater VO_{2max} values when compared to cycle protocols (30) (26). This difference is attributed to a larger recruitment of exercising skeletal muscle mass, cardiac output (5D) and arterio-venous O_2 difference, vascular conductance, and a lower rate of carbohydrate oxidation leading to a less severe development of metabolic acidosis at submaximal intensities (27-32).

In the present study subjects were taken from families where only single parent [mother/father] was hypertensive. This was because many researchers notably Hastrup JL, et al. found that subjects with two vs. one hypertensive parents had no significant differences in cardiovascular autonomic reactivity (33).

The present study observed that the mean values of basal SBP and DBP were within normal range. This showed the subjects were apparently normotensive at rest. Similar findings were observed by Muralikrishnan K, et al. among their study population (5). As of now this present study observed that many researchers were using commonly isometric hand grip [IHG] exercise test to assess cardiovascular autonomic function in their studies despite having some demerits in this test procedure which are as follows (34, 35):

- The forearm muscles are easily fatigued if not done accurately by first or second trial.
- Results are expected to differ between male and females, between left and right (dominant and non-dominant) hands, and with age.
- The results can also be affected by the position of the wrist, elbow and shoulder.

- The standardized protocol for measuring grip strength in different healthcare settings is not established. Therefore, results could be variable in different research settings.

On the other hand, Ciolac EG, et al. were used maximal graded exercise [GXT] test, that means more than 75% VO_{2max} was performed {target heart rate to be achieved ≈180 beats/minutes} on a programmable treadmill (TMX-425 Stress Treadmill; Tarck Master; Newton, KS, USA) in a temperature-controlled room (21-23ºC) with a ramp protocol until exhaustion (6). They observed sympathetic hyperactivity due to increase in plasma norepinephrine level during rest, exercise, and 10 minutes after exercise test and increased plasma epinephrine level during exercise and recovery in young women having parental history of hypertension. Although maximal graded exercise is highly accurate testing process for assessing maximal aerobic capacity, the role of such testing is limited in people whose performance may be limited because of pain or fatigue rather than exertion and in cases where maximal exercise testing is contraindicated (12).

The present study observed higher mean value of spectral components of HRV at recovery period after sub-maximal aerobic exercise compared to resting state. Similarly, Gupta N, et al. observed a significant increase in LF_{nu} and a significant decrease in HF_{nu} 5 minutes after IHG test in NOHP (35). Pai SR, et al. (36) had also shown reduced parasympathetic tone during recovery period in NOHP by using cold presser test in a sample size of 67. Although not only hypo-responders versus hyper-responder's skewed data exists in smaller sample size but also incorrect measurement of blood pressure is a common problem during this test procedure. It is also difficult to keep water temperature in correct range (4-10°C) in room temperature (37).

Moreover, spectral components of HRV in present study had shown no significant difference between the two groups at rest which could be due to masking effect as it was evidenced by Chaudhry K, et al. (38). Although recovery phase analysis had shown significant difference between these two-study population, higher mean values of LF_{nu}, LF/HF ratio and lower HF_{nu} were observed among NOHP compared to NONP which were like the study of Ciolac EG, et al. (6) in women NOHP. These findings could be the supportive evidence in reliability of data obtained from single bout of submaximal aerobic exercise to evaluate and unmask autonomic dysregulation in NOHP. This exercise program would not only be helpful to avoid undue strain but also safe for the study subjects during procedure.

On the other hand, greater resting HR (RHR) and delayed HR recovery (HRR) among NOHP in the present study might be due to higher norepinephrine spill over because of sympathetic reactivity in them (6).

All these data might be indicative of sympathetic hyper-responsiveness and reduced vagal reactivation on recovery from sub-maximal aerobic exercise test in NOHP subjects. This lower HRV might be supportive evidence for sympathovagal imbalance (SVI) and pointed towards future risk of hypertension among female NOHP (6, 9, 18). Over and above this present study also observed that female NOHP had significantly decreased in total power (TP) at recovery period compared to NONP subjects. TP could be related to the intricate interplay between the parasympathetic and the sympathetic divisions of the autonomic nervous system mostly indicated parasympathetic potency of cardiac modulation as TP: 2/3 HF + 1/3 LF) (39). Attenuation in TP at recovery period might be indicative of an additional risk factor for developing subsequent hypertension and coronary artery disease in female cases (40). Finally, this study could not find any significant difference between RHR and HRR in both groups. There are several HR regulatory mechanisms for humans (41). As the authors didn't measure neither cardiovascular hemodynamic parameters like ejection fraction, cardiac output nor blood level of catecholamines like epinephrine, norepinephrine as well as hormonal status like oestrogen, progesterone, cortisol and emotional as well as nutritional status during the present study sessions, so proper explanation for this result was beyond the scope of this current research area.

Limitation

The sample size of this study was small. Larger sample size with a long-term follow-up would have resulted in better establishing the outcome of this short-term study.

Conclusion

Study concluded that exercise at 50% of VO_{2max} was reliable to implement a sub-maximal load to evoke substantial cardiac autonomic modulation. In addition to that apparently healthy normotensive female offspring of hypertensive parents exhibit impaired cardiac autonomic modulation after exercise. This lower HRV [higher LF/HF ratio] may be an early marker of cardiac autonomic alteration in subjects with a genetic predisposition to hypertension. Early intervention by physician and lifestyle modification can delay or avoid the future risk of hypertension in them.

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