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Physiology

EVALUATION OF CARDIAC AUTONOMIC REACTIVITY AMONG YOUNG HEALTHY MALE OFFSPRING OF HYPERTENSIVE PARENTS IN RESPONSE TO AEROBIC EXERCISE: A CROSS-SECTIONAL STUDY

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ABSTRACT

BACKGROUND: The present literature suggests that the interaction of both genetic predisposition and the environment are integrally involved with the future development of hypertension in normotensive offspring of hypertensive parents (NOHP). The key marker for the future development of hypertension in them is heightened cardiovascular reactivity to mental stress and exercise test. Compare to maximal, supra-maximal and high intensity chronic exercise, assessment of cardiac autonomic response among male NOHP at rest and during recovery phase of single bout of sub-maximal aerobic exercise has been given little attention till date.

OBJECTIVE: The aim of this study was to evaluate the cardiac autonomic reactivity among young male NOHP in response to sub-maximal aerobic exercise.

METHODS: An observation and cross-sectional study was conducted on 50 young healthy male subjects aged 18-25 years who were divided in two groups: normotensive offspring of hypertensive (NOHP) and normotensive offspring of normotensive parents (NONP) in 1:1 ratio. Blood pressure (BP) was recorded at rest and immediately after termination of exercise. A short-term heart rate variability (HRV) test was conducted 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. BP, Heart rate (HR) [basal and recovery], rate pressure product (RPP) and HRV frequency domain Indices (FDI) such as normalized LF (LFnu), normalized HF (HFnu), LF-HF ratio and total power (TP) were analysed using Graph Pad Quickcalc software.

RESULTS: Significantly higher SBP and DBP were noted immediately after termination of exercise among NOHP compared to NONP. Increased LFnu and LF/HF ratio as well as decreased HFnu were observed in NOHP subjects in comparison to NONP population both at basal state and during recovery phase after exercise. In addition to that, a significant negative correlation between TP and RPP [r: −0.486; p: 0.013] was there among NOHP at rest.

CONCLUSION: Study indicated that autonomic dysfunction in NOHP manifested in the form of increased sympathetic activity and vagal inhibition and overall sympathovagal imbalance (SVI). Attenuated parasympathetic potency of cardiac modulation substantially linked to increase myocardial workload and oxygen demand in NOHP even at rest. Hence impaired cardiac autonomic modulations in healthy young male NOHP could lead to develop hypertension in future.

KEYWORDS : HRV, Sub-maximal exercise, male NOHP.

INTRODUCTION:

Essential hypertension (HTN) is a major contributor to the global non-communicable disease burden and also the commonest cardiovascular disease (CVD) as well as the worldwide leading cause of morbidity and mortality[1,2]. Especially, Asian Indians have been reported to be at increased risk of diabetes, hypertension and heart diseases[3,4] due to genetic predisposing factors as well as changes in lifestyle habit[5-7]. Researchers had shown increased vasoconstrictor tone of systemic vasculature as a result of sustained sympathetic hyperactivity is one of the major mechanism for genesis of essential hypertension[8-10]. Furthermore many studies in recent past documented hereditary nature of essential hypertension[11]. The risk of inheritance of essential HTN has positive relation with the number of hypertensive relatives. When a person has a first-degree hypertensive relative, then the risk of developing HTN is double than that of the general population. The risk increases up to four folds when the number of first-degree relatives of hypertensive subjects rises[12,13]. Hemodynamic, metabolic, neurohumoral abnormalities and increased concentration of biomarkers may have a key role in the development of HTN in non-hypertensive offspring of hypertensive parents[14,15], but exact mechanism is yet to be established. Although several researchers had been used various intensity exercise test as a physiological stressor to evoke occult cardiovascular abnormalities that are not detected at rest in normotensive subjects[16-19], there is paucity of data on the nature of autonomic modulation both at basal level and at recovery state after sub-maximal aerobic exercise that slowly leads to the progression from normotensive state into the state of hypertension among young healthymale NOHP.

Spectral analysis of HRV has been used as a sensitive tool for assessment of autonomic impairment in various clinical disorders including primary hypertension[20]. Many recent studies had been used spectral components of HRV to assess sympathovagal imbalance (SVI) among NOHP mainly at rest and immediately after stress tests[21-23]. Although the changes of frequency domain indices (FDI) of HRV at recovery state in response to submaximal aerobic exercise test among male NOHP is yet to be established till date.

AIM:

The aim of this study was to evaluate the cardiac autonomic reactivity among young adult male NOHP at rest and at recovery period after session of single bout of submaximal aerobic exercise.

METHODS: An observation and cross-sectional study was conducted on 50 healthy male 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 male 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/ 90mm of Hg as per JNC 8 guidelines)[24] 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[25].

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.

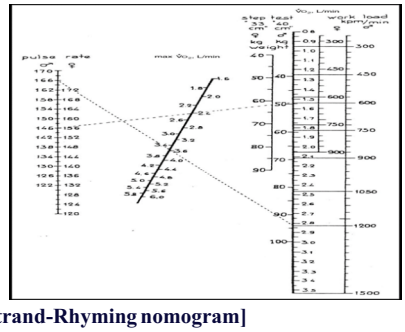
Whereas exclusion criteria were: 1. Smokers, addicts & any drug intake on a regular basis that affects autonomic nervous system.

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 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. 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, BP was recording manually by aneroid sphygmomanometer on 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[figure 1][26,27] till the pulse rate (PR) achieved 128 beats/minute which was monitored by pulse-oximeter as because Astrand-Rhyming nomogram [figure 2]had shown that 50% of VO_{2max} sub-maximal workload could be achieved by getting this PR[28,29] {according toAstrand 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[29].

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][30,31]



[Fig 2: Astrand-Rhyming nomogram]

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

Frequency domain indices (FDI) of HRV of this study were:
1. Normalized LF power (Lfnu)
2. Normalized HF power (Hfnu)
3. LF-HF ratio
4. Total power (TP)

Rate pressure product (RPP) was calculated using the formula: RPP = systolic pressure × heart rate × 10^{-2}.[32]

STATISTALANALYSIS:

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 .Followed by unpaired t-test was used for comparing continuous variable data between NOHP & NONP group (where n=25 in each) by using Graphpad Quickcalc Software,California USA. Pearson's Correlation Coefficient analysis had been done in Microsoft Excel Sheet to get r and p values were calculated by using Graphpad Quickcalc. Statistical significance was assigned at $P < 0.05$.

RESULTS AND ANALYSIS

Table 1: COMPARISON OF DIFFERENT STUDY PARAMETERS BETWEEN NOHP AND NONP AT RESTING STATE

VARIABLES	NOHP [n=25]	NONP [n=25]	t value	p value
AGE(years) (Mean ±SD)	19.16±1.491	19.36±0.907	0.573	0.569
BMI (kg/m^2) (Mean ±SD)	24.66±4.111	23.529±4.532	0.924	0.360
WAIST-HIP RATIO (Mean ±SD)	0.859±0.052	0.876±0.088	0.831	0.409
RESTING HEART RATE (RHR) (beats/min) (Mean ±SD)	79.2±12.913	81.08±12.893	0.515	0.608
SBP(mmHg) (Mean ±SD)	123.2± 14.047	122.48±13.469	0.185	0.854
DBP(mmHg) (Mean ±SD)	76.08± 10.731	77.52±7.858	0.541	0.590
LF_{nu} (Mean ±SD)	58.745± 13.042	48.549±14.473	2.616	**0.011***
HF_{nu} (Mean ±SD)	41.284± 13.028	51.434±14.582	2.595	**0.012***
LF/HF (Mean ±SD)	1.713±1.011	1.132±0.751	2.305	**0.025***
TP (ms^2) (Mean ±SD)	745.752± 429.931	527.358±381.191	1.900	0.063

Table 1 had shown that at rest

1] Mean values of LF_{nu}, LF/HF ratio were significantly higher and mean value of HF_{nu} was lower among NOHP compared to NONP population.

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

Table 2: COMPARISON OF DIFFERENT STUDY PARAMETERS BETWEEN NOHPAND NONP AFTER EXERCISE.

VARIABLES	NOHP [n=25]	NONP [n=25]	t value	p value
SBP (mmHg) (Mean ±SD)	131.44±11.937	122.88±16.408	2.109	**0.04***
DBP(mmHg) (Mean ±SD)	82.4±9.591	77.28±7.458	2.107	**0.04***
HEART RATE RECOVERY(HRR) (beats/min) (Mean ±SD)	82.24±14.234	82.48±13.626	0.060	0.951
LF_{nu} (Mean ±SD)	64.145±10.279	49.969±15.710	3.775	**0.0004***
HF_{nu} (Mean ±SD)	35.918±10.237	50.063±15.747	3.765	**0.0005***
LF/HF (Mean ±SD)	2.028±0.932	1.266±0.965	2.839	**0.006***
TP (ms^2) (Mean ±SD)	813.298± 669.048	569.049 ±340.683	1.626	0.110

Table 2 had shown that after exercise

1] Mean values of SBP, DBP, LF_{nu}, and LF/HF ratio were

significantly higher and mean value of HF_{nu} was lower among NOHP compared to NONP population.

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

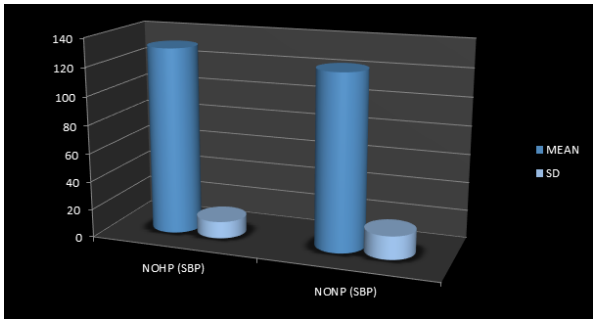


FIG 3: COMPARISON OF POST EXERCISE SBP BETWEEN NOHP AND NONP

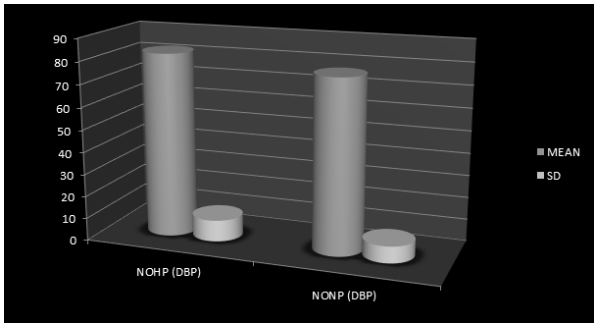


FIG 4: COMPARISON OF POST EXERCISE DBP BETWEEN NOHP AND NONP

3. CORRELATION BETWEEN TP AND RPP AMONG NOHP AND NONP POPULATION AT REST

STUDY POPULATION	TP (ms^2) (Mean ±SD)	RPP (mmHg/min) (Mean ±SD)	r value	p value
NOHP (Mean ±SD)	745.752±429.931	97.884±20.923	− 0.486	**0.013***
NONP (Mean ±SD)	527.358±381.191	99.582±20.462	− 0.166	0.427

Table 3 had shown that at rest:

1] There was moderate significant negative correlation between TP and RPP in NOHP population.[Fig:5]

2] There was no significant correlation between TP and RPP in NONP population.[Fig:6]

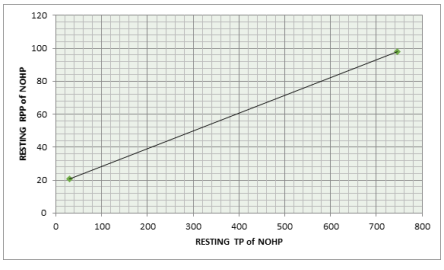


FIG 5: CORRELATION BETWEEN TP AND RPP AMONG NOHP AT REST

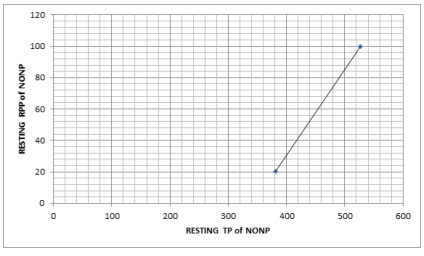


FIG 6: CORRELATION BETWEEN TP AND RPP AMONG NONP AT REST

DISCUSSION:

In our study we had chosen fixed intensities targeting percentage of VO_{2max} for all the participants throughout the testing condition forming homogenous groups for power values. As there are no "gold standards" for training load prescription till date[33], 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[34].

The present study observed that the mean values of basal systolic and diastolic blood pressure (SBP and DBP) were within normal range as well as no significant difference was there between case and control groups. Similar findings were observed by Muralikrishnan K, et al.[21]. These findings documented that the groups were normotensive at rest and apparently there was no difference between case and control groups.

The spectral components of HRV analysis had shown that LF normalised unit (LF_{nu}) was significantly higher in NOHP compared to NONP even at resting state. It is worth to note that LF component of HRV to be a strong predictor of future hypertension in men by means of sympathetic hyperactivity[35]. Increased in LF_{nu} was also observed in the recent onset hypertension[36].

In the present study basal HF_{nu} was significantly decreased in the NOHP compared to NONP, although total autonomic power (TP) was not significantly different in them. This finding was in accordance with that earlier study conducted by Muralikrishnan K, et al. where HF_{nu} was significantly diminished in the study group at rest[21]. As HFnu indicated parasympathetic activity of autonomic nervous system[35], hence the present study indicated attenuated early cardiovascular vagal tone in NOHP even at rest. Vagal tone is not only an important determinant of cardiovascular health but also has insightful influence on the heart rate, cardiac output as well as on blood pressure. Persons having attenuated vagal tone are more prone to develop various cardiovascular diseases including hypertension[35].

Moreover increased LF/HF ratio in NOHP triggered early sympathovagal imbalance in them even at resting condition which might be indicative of future risk of hypertension as several researchers had shown in recent past[21].

Folkow et al. demonstrated that there was a change in the wall-to-lumen ratio of arterioles in subjects with genetic predisposition to hypertension after giving repeated episodes of stress over time, ultimately resulting in a fixed increase in peripheral vascular resistance (PVR) and future hypertension[37-39]. In support of this viewpoint, male NOHP in this study had shown a greater responsiveness to stress by means of single bout of sub-maximal aerobic exercise at 50% VO_{2max} workload compared to the other population, as manifested by higher mean systolic and diastolic blood pressure (SBP and DBP) immediately after termination of exercise. Four possible physiological mechanisms were postulated for the exercise induced BP changes:

1] Withdrawal of sympathetic tone and a rebound increase in vagal tone occur immediately after exercise. Abnormalities of autonomic control could extend into the early recovery phase of exercise resulting in elevated recovery blood pressure in those at risk of hypertension[40,41].

2] Increase in endothelin-1 secretion might also be important in development of hypertension. There is also enhanced vasoconstrictor response to endothelin-1 during exercise. This might be the result of impaired release of NO or abnormality in endothelin receptor[42,43].

3] The kidney may play a crucial role in development of genetic hypertension. The possible mechanism would be early changes in glomerular function and vasoactive hormone excretion[44,45].

4] There might be the altered baroreceptor sensitivity. The baroreceptor reflex is a negative feedback system acting to reduce BP variability, with the adaptive end of preserving transcapillary pressure for maintains vital tissues which may cause increased BP response[46].

Furthermore the present study had shown significantly increase in mean values of FDI such as LF_{nu}, LF/HF ratio and decrease HF_{nu} among NOHP also during last 5 minutes of 15 minutes recovery phase after exercise. Chauhan A et al. [22] also had shown similar autonomic changes after aerobic exercise indicating future risk of hypertension in males.

RPP is an indirect measure of myocardial load and oxygen consumption i.e MVO_2.[32] It also reflects the internal myocardial work performed by the heart during each beat[47]. On the other hand TP denotes parasympathetic potential of cardiac modulation [TP=2/3HF +1/3 LF][35]. As the degree of correlation of TP with RPP was significantly negative only for NOHP population (Table 3) which was an important finding of this present study, hence resting myocardial energy expenditure could be more in these subjects. Therefore, the risk of cardiovascular dysfunctions associated with NOHP subjects[8-10] may possibly be linked to the level of parasympathetic potency and RPP even at rest. As BP measurement was not done at recovery phase while recording HRV, so correlation of TP and RPP could not be analysed at that time in study subjects which could be a drawback of this study.

ADVANTAGES

1] Well-matched controls;
2] Homogeneity between the two groups in regard to age, sex, baseline blood pressures, and numerous other factors.

LIMITATIONS

1] Grouping of normotensive subjects was done only on the basis of history of hypertension in one parent [NOHP and NONP]. This is because many researchers notably Hastrup JL et al.[48] found that subjects with two vs. one hypertensive parents have no significant differences in cardiovascular reactivity, suggesting that only two groups were necessary. However, Manuck SB et al.[49] recommend using three groups, one group with both normotensive parents, one with one hypertensive parent, and one with two hypertensive parents
2] We recorded the blood pressure at rest and immediate after exercise using aneroid sphygmomanometer. But we could not record blood pressure changes during exercise as the aneroid BP instrument we used in this study was movement sensitive. We did not try to obtain dynamic BP recording by using GPS sports watch (Polar 360 Fitness Tracker) as none of the previous researchers had included this procedure in their study protocol and so no interpretation was available.
3] We didn't measure neither cardiovascular hemodynamic parameters like ejection fraction, cardiac output nor blood level of catecholamines like epinephrine, norepinephrine as well as ovarian hormonal status like estrogen, progesterone during our study sessions. This could have provided us valuable data regarding appropriate adjustment of the milieu interior.
4] Larger sample size with a long term follow-up would have resulted in better establishing the outcome of this short term study.

CONCLUSION:

Study indicated that autonomic impairment in male NOHP manifested in the form of increased sympathetic activity and attenuated vagal response as well as overall sympathovagal imbalance (SVI). Diminished parasympathetic potency of cardiac modulation substantially linked to increase myocardial workload and oxygen demand in them. Hence impaired cardiac autonomic modulations in healthy young male NOHP could lead to develop hypertension in future. So they are advised that life style modifications should be adopted for achieving effective autonomic homeostasis.

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