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RESEARCH ARTICLE

The study of cardiovascular sympathetic reactivity in unmasking hypertension in offsprings of hypertensive parents

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ABSTRACT

Background: Hypertension is one of the major public health challenge in the world. Early detection of hypertension may enable an individual to enjoy a healthy life by lifestyle modifications. It is well established that genes, environment and its interactions are important in the pathogenesis and risk of hypertension. Studies have shown an association between excessive blood pressure (BP) reactivity to cardiovascular sympathetic tests and incidence of subsequent hypertension. Cold Pressor test (CPT) and isometric handgrip test (IHG) are commonly used test for cardiovascular sympathetic reactivity. **Aims and Objectives:** The aim is to explore the cardiovascular reactivity to stress (CPT and IHG) and the recovery time after the withdrawal of the stressor in normotensive offspring of hypertensive parents. **Materials and Methods:** The study is an observation case–control study with a total of 40 normotensive subjects of age 17–25 years who have a family history of hypertension and age and sex-matched 40 normotensive subjects with no family history of hypertension were taken as control. Systolic BP (SBP), diastolic BP (DBP), and mean BP (MBP) were measured during rest, during IHG test, 5 min after IHG in the recovery phase, during CPT and 4 min after CPT in the recovery phase. **Result:** In our study, the SBP, DBP, and the MBP during resting stage were significantly higher in the normotensive offspring's of hypertensive parents as compared to control group. There were significant increases in the systolic, diastolic, and the MBPs during the isometric exercise and CPT in both the groups. Recovery to the baseline after cardiac sympathetic reflex tests such as IHG and CPT also was slow among the positive family history groups compared to participants with a negative family history of hypertension. **Conclusion:** Hypertension has a genetic disposition. The subjects from the hypertensive families showed greater and prolonged responsiveness to sympathetic stimulation in comparison to the subjects from the non-hypertensive families, indicating the hyperresponsiveness of the sympathetic nervous system to stressor stimuli in the offspring of hypertensive adults.

KEY WORDS: Cold Pressor Test; Hypertension; Isometric Hand Grip Test; Offspring's

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INTRODUCTION

Hypertension has emerged as one of the biggest public health problem in the world because of high frequency and associated kidney and cardiovascular diseases. In India, the prevalence of cardiovascular disease is 69.9 and 59.9 per 1000 in males and females in urban population while in rural population it

is 35.5 and35.9 per thousand and about 24% of all coronary heart disease deaths can be attributed to hypertension alone.[1,2] In India, the prevalence of hypertension is alarming and is expected to be 159.46 per 1000 population by 2020.[3]

Early detection of hypertension may enable an individual to enjoy a healthy life by lifestyle modifications.[4] The risk of hypertension is doubled with family history if one first degree relative is hypertensive and if two first degree relatives are hypertensive it increases to 4 times.[5] Essential hypertension is a hereditary disease, and it is known that genetic factors and its interactions with the environment determine the risk of hypertension and blood pressure (BP) of an individual. Studies have shown that hypertension is usually associated with overactivity of the sympathetic nervous system, but in some individuals, the response to sympathetic stimulation has been reported to be more profound in normotensive as well as a hypertensive population which can be attributed to the genetic factors.

The reactivity of BP in response to stress has been reported to be a marker for subsequent development of hypertension.[6] Studies have shown an association between the excessive reactivity of BP to cardiovascular sympathetic tests and increased incidence of hypertension in future. Cold pressor test (CPT) and isometric handgrip test (IHG) are commonly used test for cardiovascular sympathetic reactivity. Menkes *et al*., in a prospective study, reported that risk of developing hypertension later in life was higher in subjects with increased responses to BP during CPT.[7] Studies have demonstrated that in hypertensive patients reduced sympathoexcitatory response to a CPT is profound and the similar response can be observed in young subjects with a family history of hypertension.[8] Garg *et al*. reported that greater reactivity to the IHG in subjects with a positive family history of hypertension.[9]

In response to a stressor, the sympathetic nervous system triggers a rise in BP and heart rate. They usually return to their normal baseline levels within a short duration of time after the stressor is withdrawn.[10] In susceptible individuals, the BP and heart rate are elevated for a longer duration. The persons who show higher cardiovascular reactivity to a stressor in CPT or IHG and rate of recovery is slower after the stressor causing this sympathetic stimulation is withdrawn may be at high risk of developing subsequent hypertension in future. Studies support the hypothesis that individuals who are at high risk of developing hypertension may have an increased cardiovascular response to induced stress at a young age and sympathetic nervous system is an important factor in the pathophysiology of hypertension.

Despite the prognostic implications and lot of interest shown in this subject, only recently has there been more focus on the genetic component of BP responses to cardiovascular reactivity and the correlation between BP reactivity and its recovery to baseline after stress, but still many questions in this field remained unanswered. A better understanding of the influence of heredity factors on the development of subsequent hypertension may affect the therapeutic intervention and lifestyle alterations.

Hence, in the present study, the aim is to observe the BP and heart rate reactivity to cardiovascular sympathetic stress tests and its recovery after the withdrawal of the stressor in normotensive subjects with family history of hypertension and normotensive subjects with no family history and identify its use in unmasking hypertension in high-risk individuals.

MATERIALS AND METHODS

The study design was observational and case–control. The study was conducted in the Physiology Department, Late Shri Lakhiram Agrawal Memorial Government Medical College, Raigarh, C.G. after approval from the Institutional Ethical Committee. The subjects were recruited among the medical students after obtaining explained written consent and the data were collected from September 2015 to October 2015. A total of 40 normotensive subjects of age 17–25 years with a family history of hypertension in first- and second-degree relatives as per JNC-7 and World Health Organization were recruited for the study. Age- and sex-matched 40 normotensive subjects with no family history of hypertension were taken as control.

The subjects having a history of smoking, hypertension, known case of myocardial infarction, heart disease, renal disease, or any history of medication were excluded from the study. History, general and systemic examination was carried out for all the subjects.

The participants were instructed not to take tea, coffee or any beverages 1 hour before the recording. Subject's height and weight were recorded.

Resting Pulse Rate

Baseline pulse rate was measured after a rest of 10 min in supine position, and radial pulse rate was recorded in supine position and expressed as beats/min.

Resting BP

After rest in supine position baseline, BP was measured with a mercury sphygmomanometer in mmHg. For assessing sympathetic reactivity, the tests done were:

IHG Test

In this test, the subject was asked to squeeze the hand dynamometer maximum strength by dominant hand. Then the subject was asked to hold the dynamometer constant

at 30% of the maximum voluntary contraction achieved for 5 min. The BP and heart rate were measured in the non-exercising hand during the test. This sustained muscle contraction will cause a rise in heart rate as well as systolic BP (SBP) and diastolic BP (DBP). If the rise in DBP is <10 mm Hg it is defined as abnormal, between 11 and 15 mm Hg as borderline and above 16 mm Hg is considered as normal. After 5 min of completing the exercise, the BP and pulse were again measured.

Then 5 min rest was given to the subjects.

CPT

Cold water of temperature maintained at 4°C in a wide-mouthed insulated container was prepared. The subject was asked to submerge the hand in the container up to the wrist. BP and pulse were recorded at the level of pain threshold if it occurs before 1 min or at the end of 1 min of immersion of hand in cold water. A warm cloth was provided to the subject, and BP and heart rate were again measured 4 min after removal of the hand from cold water.

Statistical Analysis

Statistical analysis was done by SPSS software. The statistical tests used were as per data requirement and our objectives of the study. Data were presented as a mean ± standard deviation. One-way ANOVA was used for inter- and intra-group comparisons in two groups with 5% level of significance. $P < 0.05$ was considered to be statistically significant.

RESULTS

The subjects in Group I which consisted of subjects with no family history of hypertension had a mean age of 20.35±2.89 while in Group II which consisted of subjects with family history of hypertension has mean age 20.1±2.91. Table 1 depicts the SBP, DBP, and mean BP (MBP) in Group I and Group II during rest, during IHG test, 5 min after IHG in the recovery phase, during CPT, and 4 min after CPT in the recovery phase. In comparison to Group I SBP, DBP, and MBP were more in Group II at baseline, and it is statistically significant. Then, during IHG and CPT, BP increased in both the groups. The difference between the systolic pressure in Group I and Group II decreased from 8.5% at baseline to 6.1% during IHG and 6.29% during CPT while in recovery phase it was 10.63% in IHG and 9.73% in CPT. However, there was an increase in the difference between diastolic and MBP between Group I and Group II during IHG from 9%–15.75% in DBP to 8.8–11.59% in MBP while during CPT difference in DBP and MBP were 14.57% and 10.98%, respectively. This difference further increased during recovery phase in DBP in both IHG and CPT to 23.29% and 24.93%, respectively.

Table 1: BP in both group during various stages

Groups	SBP	DBP	MBP
Group I			
Baseline	109.2±2.11	71.2±2.07	83.87±1.37
During IHG	120.4±2.41	78.8±2.51	92.67±1.64
5 min after IHG	110.2±2.11	71.8±2.07	84.87±1.37
During CPT	122.8±2.55	80.20±2.07	94.40±1.40
4 min after CPT	110.2±2.11	72.20±2.07	84.80±1.56
Group II			
Baseline	119.35±2.54*	78.48±1.78*	92.1±1.33*
During IHG	128.38±2.47*	92.60±2.84*	104.53±1.80*
5 min after IHG	122.80±2.55*	90.00±2.40*	100.93±1.53*
During CPT	131.80±2.55*	92.80±2.51*	105.80±1.71*
4 min after CPT	121.80±2.55*	91.20±2.67*	101.40±1.69*

Group I: Without family history of hypertension, Group II: With family history of hypertension. *P<0.001 versus Group I.
BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure, CPT: Cold Pressor test, IHG: Isometric hand grip

DISCUSSION

In our study at the baseline, the systolic and DBP were statistically higher in subjects with a family history of hypertension as compared to the subjects with no family history of hypertension. There was an increase in the systolic, diastolic, and the MBPs on the application of cardiovascular sympathetic stressor in both the groups while performing the isometric exercise as well as CPT. Our study showed that the after recovery period the BP in Group I returned to baseline but in subjects with family history of hypertension the BP was significantly higher even after the recovery phase of 5 min in both CPT and IHG. Increased concentration of metabolites such as adenosine and lactic acid is produced during isometric exercise such as IHG which stimulates the nerve ending in the muscle fibers. Thus increase discharge of Group IV (metaboreceptors) afferent fibers initiate a reflex increasing the activity of the sympathetic nervous system. This stimulation of sympathetic system cause vasoconstriction leading to an increase in the BP.[11] However, once the exercise is ceased the BP returns to baseline within 5 min in normal individuals. Similarly, during CPT in normal individuals, there is an increase in BP.[7,12,13] This is attributed to an increase in cardiac output during the first phase of the test and increase in sympathetic nerve activity of the muscle, while it increases peripheral resistance in the later phase of the test.[14] The CPT causes stress which leads to sympathetic activation and a subsequent increase in BP.[15] The cause of vasoconstriction is stimulation of the sympathetic noradrenergic fibers. Neuropeptide Y is released from the noradrenergic post-ganglionic sympathetic nerves which also cause vasoconstriction leading to arteriolar constriction resulting in increased BP.[16] These effects usually return to

baseline level within a short period of time (5 min) after the removal of the stressor.[10]

Lopes *et al*.[17] reported that baseline BP of young subjects with normal BP who has a family history of hypertension was higher than subjects with normal BP and no family history which can be attributed to increased sympathetic activity even before the isometric exercise and these results were similar to the finding in our study. Our study showed that the difference in the BP between the groups was significant suggesting that the subjects with a family history have a greater reactivity of the blood vessels to physical stress. Krzeminski *et al*.[18] also reported an increase in both the SBP and DBP on performing isometric handgrip exercise which is consistent with our study results. Bakke *et al*.[19] suggested that increase in total peripheral resistance is the main cause for the increase in MBP on performing the isometric exercise. Yamada *et al*.[20] showed that in muscle sympathetic nerve activity there is a reduction in baroreflex inhibition in adolescents with normal BP and a family history as compared to the control group. This reduction in baroreflex inhibition may lead to the increased sympathetic vasomotor tone which may cause the subsequent development of hypertension in such individuals. In addition, the subjects with a family history of hypertension during the isometric exercise and cold pressure test showed increased reactivity of the total peripheral resistance.

An imbalance of the cardiovascular sympathetic reactivity and the circulating noradrenaline is a common predisposing factor for the development of essential hypertension in subjects with family history of hypertension.[21] Due to the reduced threshold to norepinephrine, the response to norepinephrine was exaggerated in normotensive offsprings of hypertensive subjects as compared to subjects with no family history.[22] Hypertension has a genetic disposition. The subjects from the hypertensive families reported hyperresponsiveness to cardiovascular sympathetic stressors in comparison to the subjects from the non-hypertensive families, indicating the enhanced reactivity of the sympathetic system to stressor stimuli in the offspring's of hypertensive adults.

CONCLUSION

The present study has shown that the increase in the response of the BP profile is more in participants with a positive family history of hypertension compared to participants with a negative family history of hypertension. Recovery to the baseline after cardiac sympathetic reflex tests such as IHG and CPT also was slow among the subjects with positive family history compared to participants with no family history of hypertension. This study may suggest that the subjects with a familial predisposition to primary hypertension have prolonged effect of stress on BP and cardiac sympathetic reactivity tests can be used in detecting individuals with high risk of developing subsequent hypertension in their future life. These tests may thus identify a subgroup of individuals with an underlying physiological change that predisposes them to hypertension decades later. Preventive interventions may be particularly warranted in these individuals and may help in the unmasking of hypertension early.

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