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Original Research Article

A Study of Cardiovascular and Adrenocortical Stress Reactivity in Children of Hypertensives

Suchitra B[1*], Malarmannann K B[1**], Subha M[2*], Varshney V P[3#], Bedi M[4#]

[1]Senior Resident, [2]Research Scholar, [3]Director Professor, [4]Professor,
[*]Dept of Physiology, Jawaharlal Institute of Post Graduate Medical Education & Research (JIPMER), Puducherry.
[**]Dept of Emergency Medicine, Shri LakshminarayanaInstitute of Medical Sciences (SLIMS), Puducherry.
[#]Dept of Physiology, Maulana Azad Medical College (MAMC), New Delhi.

Corresponding Author: Suchitra B

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ABSTRACT

Background: Stress plays an inevitable role in today's modern life and it leads to various physiological and pathological reactions through activation of the Limbic-Hypothalamo-Pituitary-Adrenal axis and secretion of Cortisol which modulates vascular reactivity. Hypertension is known to be one of the commonest reactions to stress, with increased cardiovascular morbidity and mortality. The disease process starts much earlier than it is manifested clinically, hence it is necessary to find out the persons at risk for hypertension as early as possible and to introduce early lifestyle modifications to prevent them from developing hypertension.
Objective: This study assessed and compared the cardiovascular reactivity and adrenocortical reactivity in children aged 14 to 18 years of hypertensive parents (Study group, n=30) with age, sex and BMI matched children of normotensive parents (Control group, n=30) exposed to three different stress tests.
Methods: Cardiovascular reactivity in terms of change in heart rate and blood pressure from the baseline and Adrenocortical reactivity in terms of change in serum cortisol level from the baseline were measured after performing three stress tests namely mental arithmetic test, isometric handgrip test and cold pressor test. Results: The mean ± S.D. for change in serum cortisol in the study group (86.5 ± 23.99) was significantly higher ($p < 0.05$) than that in the control group (69.62 ± 30.92), whereas, the mean ± S.D. for the change in heart rate and blood pressure was not found to be significant between the two groups.
Conclusion: Our study showed that there is a significant increase in the adrenocortical reactivity to stress than the cardiovascular reactivity in subjects with family history of hypertension thus warranting early lifestyle modifications and further follow up for monitoring their blood pressure status and hypertension propensity.

Keywords: Hypertension, Children of hypertensive parents, cardiovascular reactivity, adrenocortical reactivity, Serum Cortisol.

INTRODUCTION

Hypertension has been known since time immemorial to be one of the major causes of cardiovascular morbidity and mortality. Although the disease process starts earlier, clinical manifestations do not usually appear until late middle age. An increased cardiovascular reactivity to stress is postulated to be one of the risk factors for hypertension. [1] Stress either emotional or physical has become a part of day to day

modern life and it induces various cardiovascular and other physiological responses by stimulating the *Limbic-Hypothalamo-Pituitary-Adrenal* axis *via* cortisol. [2] Cortisol assists in regulating blood pressure and cardiovascular functions. It also helps in responding to and coping with stress, trauma and environmental extremes. [3] Cortisol plays a major permissive role in maintaining cardiovascular activity through the Catecholamines and its presence enhances stress responses of the cardiovascular system. [4]

Hypertension is occurring at an earlier age in the modern era, so there is a need to identify those persons who are at risk and to initiate preventive measures at the earliest. The prevalence of essential hypertension (EH) and further progression to cardiovascular disease is constantly increasing in adolescent population. Persons prone to develop hypertension in future, manifest an altered physiology at a younger age itself. [5] Hence it is important to identify children and adolescents who are at increased risk of developing essential hypertension as adults and to initiate the strategies for prevention of essential hypertension in childhood itself. Excessive cardiovascular reactivity to stress may have a pathophysiological role in essential hypertension. [6] EH results from an altered interaction between various mechanisms involved in normal blood pressure regulation. It is also suggested that these mechanisms are operative in the prehypertensive state itself. Young prehypertensive individuals manifest an inherent central hyper reactivity to stressor stimuli. [7,8]

There are a number of studies which tend to show a strong association between cardiovascular reactivity to stress and future hypertension, thus supporting the reactivity hypothesis, which states that exaggerated physical and psychological responses to stress identify subgroup with increased cardiovascular disease risk [9-11] Most of the studies done so far have shown increased cardiovascular reactivity (CVR) to stress may lead to future hypertension. And very few studies have been done to explore the relationship between increased Cortisol secretion or adrenocortical reactivity (ACR) to stress and future hypertension.

Most of the studies in the past have been done in the hypertensive patients themselves, to predict stress reactivity and not in their offspring. So in the present study we made an attempt to find out whether the adolescent age groups off springs of hypertensive parents are showing increased cardiovascular reactivity to stress, to find out whether this increased reactivity can be used as a predictor of developing future hypertension. A concomitant study of cardiovascular and adrenocortical reactivity to different stresses in children of hypertensive parents is hardly available in India. Therefore, our objective was to assess the heart rate and blood pressure responses before and after mental arithmetic test, isometric hand-grip test and cold pressor test in adolescent children (14-18 years) of diagnosed hypertensive parents, to study the serum Cortisol levels before and after the above tests in these children and to compare and correlate the above findings with those of normal subjects.

MATERIALS AND METHODS

This study was conducted in the Department of Physiology, Maulana Azad Medical College, and New Delhi. The study was conducted after institutional ethical committee approval and informed written consent from the parents and acceptance from the children. Hypertensive patients who attended the Medicine outpatient department at LN hospital, New Delhi were counselled to bring their children aged 14 to 18 years to the Physiology department to undergo the present study.

Study group included adolescent children aged 14-18 years with normal

BMI (19 to 25 kg/m^2) and at least one of the parents had essential hypertension. Exclusion criteria for study group were children with history of any co-morbid conditions like preexisting Hypertension, Diabetes mellitus, Bronchial asthma, any renal disease, Neuro-endocrine disorders *etc,* children under medication, children with habit of taking alcohol, tobacco, drug abuse and children with history of any recent illness.

Control group included normal healthy children aged 14 to 18 years of either sex with no family history of hypertension matched for age, sex and anthropometrically with those of the subjects.

Subjects were abstained from tea, coffee, chocolate, and ice-cream for at least 12 hours prior to testing. The tests were performed at ambient temperature after obtaining the consent from their parents and assent from the participants. Fasting blood sample was taken to assess general health status along with baseline serum cortisol levels. Each subject was given a thorough work up for history and physical examination to fulfill the inclusion and exclusion criteria.

Stress tests

In order to allay anxiety and apprehension associated with the testing, the subjects were made to sit relaxed and were explained the purpose of the study and also the various procedures of the tests to be used. Adequate rest was given between each stress test for the blood pressure and heart rate to come back to baseline levels.

1. Mental arithmetic test: [12]

The subject was made to sit comfortably in a chair and the test procedure was clearly explained to him. Resting blood pressure and heart rate was noted and recorded. The subject was asked to subtract 13 from a four digit number say starting from 2479 and was asked to do the calculation in mind. They were made to say the answer as fast as possible with a metronome made noise at every 30 seconds; again they have to continue subtracting 13 from the answer and so on. This was repeated continuously for 5 minutes. Mistakes if any were corrected. Blood pressure and heart rate were noted at 0, 2 and 5 minutes and the findings recorded.

2. Isometric hand grip test: [13]

This test was carried out in a controlled setting using hand grip dynamometer developed by INCO, Ambala. The subject was made to sit comfortably in a chair with his/her dominant arm flexed at the elbow and the forearm rested on the arm rest of the chair and then the subject was asked to grip the strain gauge dynamometer with their maximal strength. Three successive trials were performed by the subject and the maximum of the three values was taken as maximum voluntary contraction (MVC), following this the subjects were asked to maintain the hand grip steadily at 30% or 1/3 of the MVC for up to three minutes. During this test the blood pressure and heart rate were recorded at 0, 1 and 3 minutes from the non-exercising arm.

3. Cold pressor test: [14]

The nature of the test was explained to the subjects, as placing the hand in cold water will act as a painful stimulus, and they were reassured that the test would not do any harm. This test was done as one of the last tests, because of its unpleasant nature. The resting blood pressure and heart rate were recorded with the subject sitting comfortably in the chair. The subject was then asked to immerse his/her dominant hand 5cm above the wrist level in ice cold water maintained at a temperature of 4 to 6 degree Celsius for a period of one minute. Blood pressure and heart rate were recorded from the other arm at 30 seconds interval and noted in the proforma.

4. Test for serum cortisol: [15,16]

Before doing the stress tests (baseline or pre-test) and at the end of all the three stress tests (post-test) blood sample was collected in vacutainers and serum was

stored at –80^{o} C and quantitative determination of serum cortisol was done by *Electrochemiluminescence immunoassay (ECLIA)* method done on 'Elecsys' immunoassay analyzers.

Statistical Analysis: The collected information and readings were tabulated and appropriate statistical analysis was done by two tailed *student't' test*. Analysis was performed with SPSS software version 16.0. For each variable, data was expressed as mean ± standard deviation. Values of $p< 0.05$ were considered as statistically significant.

RESULTS

Cardiovascular parameters

The mean values ± standard deviation of the resting systolic blood pressure, diastolic blood pressure and heart rate and the corresponding changes after each stress test for the two groups are given in table 1. It was observed that the '*p*' value after applying Student t test is >0.05, hence found to be insignificant cardiovascular reactivity

Table 1: Cardiovascular changes after each stress test

	PARAMETER	STUDY GROUP (Mean ± S.D.) (n=30)	CONTROL GROUP (Mean ± S.D.) (n=30)	P-VALUE
Mental Arithmetic Test	Resting SBP (mmHg)	118.20 ± 6.65	118.00 ± 5.85	NS
	Resting DBP (mmHg)	77.67 ± 5.07	78.13 ± 5.80	NS
	Resting HR (per minute)	80.60 ± 3.91	81.07 ± 3.23	NS
	Change in SBP from resting SBP (mmHg)	10.87 ± 3.27	10.33 ± 2.58	NS
	Change in DBP from resting DBP (mmHg)	7.93 ± 1.86	7.87 ± 1.28	NS
	Change in HR from resting HR (per minute)	7.07 ± 1.36	7.27 ± 1.44	NS
Isometric Hand-Grip Test	Resting SBP (mmHg)	118.20 ± 5.08	118.53 ± 4.61	NS
	Resting DBP (mmHg)	77.20 ± 4.48	77.67 ± 4.85	NS
	Resting HR (per minute)	81.30 ± 2.54	80.97 ± 2.30	NS
	Change in SBP from resting SBP (mmHg)	16.07 ± 3.62	14.67 ± 2.59	NS
	Change in DBP from resting DBP (mmHg)	10.27 ± 1.80	10.47 ± 1.72	NS
	Change in HR from resting HR (per minute)	8.00 ± 1.29	8.20 ± 1.32	NS
Cold Pressor Test	Resting SBP (mmHg)	120.47 ± 2.66	119.67 ± 3.45	NS
	Resting DBP (mmHg)	76.80 ± 2.55	76.40 ± 1.77	NS
	Resting HR (per minute)	82.23 ± 3.34	81.77 ± 2.52	NS
	Change in SBP from resting SBP (mmHg)	8.33 ± 2.04	8.07 ± 1.34	NS
	Change in DBP from resting DBP (mmHg)	5.53 ± 1.36	5.40 ± 1.30	NS
	Change in HR from resting HR (per minute)	5.07 ± 1.64	4.93 ± 1.80	NS

*p-value > 0.05 Not Significant (NS); <0.05 Significant (S); <0.01 Highly significant (HS); <0.001 Very highly significant (VHS)

Table 2: Level of serum cortisol before and after stress tests.

PARAMETER		STUDY GROUP (n=30)	CONTROL GROUP (n=30)	P-VALUE
Baseline level	Mean ± S.D.	338.77 ± 145.55	268.53 ± 145.77	NS
	Range	101.3 - 607.2	107.7 - 551.4	
After Tests	Mean ± S.D.	425.27 ± 139.39	338.15 ± 152.64	S
	Range	166.1 - 674.2	165.3 - 611.3	*
Change from Baseline	Mean ± S.D.	86.50 ± 23.99	69.62 ± 30.92	S
	Range	50.6 - 151.4	18.2 - 130.8	*

*p-value > 0.05 Not Significant (NS); <0.05 Significant (S); <0.01 Highly significant (HS); <0.001 Very highly significant (VHS)

Adrenocortical reactivity

The data on the mean values ± standard deviation of serum cortisol are given in table 2. It was found that the mean ± standard deviation of baseline serum Cortisol level is more for the study group than that of the control group, but its statistical significance could not be established.

But at the same time serum cortisol level taken after completion of all the three stress tests was significantly more for the study group than for the control group, Also, the mean ± standard deviation value of change in serum cortisol from the baseline level is more in the study group than that in the control group and again the difference is statistically significant (Figure I) between the groups, indicating a significant adrenocortical reactivity in the children of hypertensive parents.

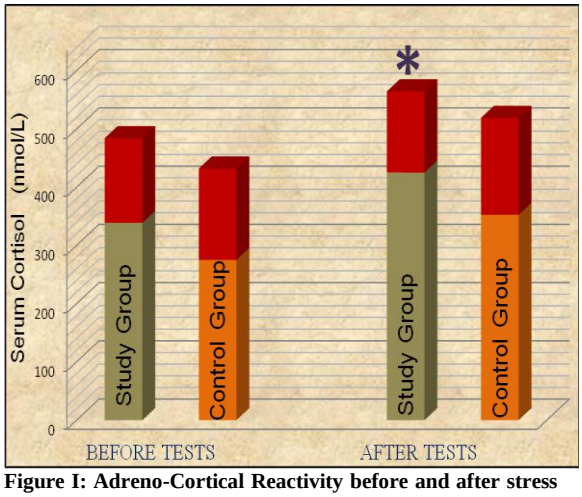

Figure I: Adreno-Cortical Reactivity before and after stress tests

DISCUSSION

In this fast paced life, most people are exposed to various stresses – either mental or physical, which can lead to various physiological adaptations to cope up. Increase in the level of various stress hormones, especially cortisol is responsible for the various physiological reactions to stress. Increase in cardiovascular reactivity to stress is one of the most common reactions to stress. Some people show high reactivity while others show low reactivity. There are ample data available linking high stress reactivity and further development of various cardiovascular complications, Hypertension is known to be one of them. [17,18]

Hypertension is one of the major causes of cardiovascular morbidity and mortality. Even as the disease process starts earlier, clinical manifestations usually appear until late middle age. Due to increase in stress levels, the age of onset of the disease is now earlier than before, making it essential for the early detection of people who could be future hypertensives, so that early preventive measures could be taken. [19] And it has been found that there is genetic susceptibility for hypertension in children with family history of hypertension. There are more data indicating that children of hypertensive parents tend to exhibit high stress reactivity influenced by both genetic and environmental factors. Although family history of hypertension itself was a meaningful predictor of change in blood pressure status on its own, high stress reactivity was shown to potentiate greatly the risk of developing elevated blood pressure. [20]

High cardiovascular reactivity to stress may play a role in the long term pathogenesis of future hypertension. There are a number of studies which tend to show a strong association between cardiovascular reactivity and future hypertension thus supporting the reactivity hypothesis and increased future cardiovascular risk. [10,19] Previous reactivity research has almost solely focused on blood pressure and heart rate responses to stress. Relatively few studies have examined Cortisol secretion in response to stress in hypertensives and persons at risk for hypertension.

In a study on off-springs of normotensive and hypertensive parents Ravogli *et al.* demonstrated no difference in reaction to stress tests. [21] In another study, Light *et al.* demonstrated that, high stress reactivity predicted increases in tonic blood pressure over a 10 year period, only if it was associated both with a positive family history and with high levels of daily stress. [22] Some studies declare that the characteristic hyper reactivity especially with respect to cardiovascular parameters to acute stimulation seem to be stable over time, as they habituate readily while other studies

linked this enhanced responsiveness to a higher incidence of cardiovascular disease. [23] Eich *et al.* suggested that the hemodynamic pattern in adults with labile hypertension includes an increased cardiac output and increase in total peripheral resistance; this hyperkinetic circulatory state is due to emotional hyper reactivity attenuated baroreceptor-sensitivity and increased adrenergic input to the heart. [24]

To date, in India we lack data linking cardiovascular reactivity and adrenocortical responsivity after applying various stresses to later development of disease processes. Most of the studies in the past have been done in hypertensive patients themselves and not in their off-spring. Some studies done in their off-spring included one or the other type of stresses. Experimental evidence to explain mechanisms directing the hemodynamic response to stress in children is quite limited.

In the present study, an attempt has been made to assess the cardiovascular and adrenocortical reactivity to different stresses, including mental and physical stresses in the children of hypertensive parents. This study comprised of 30 children in the age group of 14 to 18 years of hypertensive parents compared with 30 number of age, sex and BMI matched children with no family history of hypertension. For this study, we used three different stresses as stimuli and measured the cardiovascular reactivity in terms of change in systolic blood pressure, diastolic blood pressure and heart rate; and the adrenocortical reactivity in terms of change in serum Cortisol. The three different stress tests used were: Mental arithmetic test, Isometric hand-grip test and Cold pressor test.

Cardiovascular reactivity

Mental arithmetic test:

In the present study, with mental-arithmetic test, a little increase in systolic blood pressure, diastolic blood pressure and heart rate was observed in the study group but the control group also showed a similar rise and there was no significant difference in reactivity between the two groups with mental arithmetic test. This is in agreement with a study conducted by Manuck*et al.* in which they reported an elevated resting blood pressure but no difference in reactivity to a variety of mental stress tests. [25] Another study published by Van Egeren*et al.* demonstrated a negative relationship between memory test and response to blood pressure and heart rate variability. This is because intense sensory intake often decelerates the heart *via* vagal activation. [26]

In contrast to this study Wood *et al.* showed that hyper reactivity precedes progression to sustained hypertension and this increased response is evoked under stress - either mental or physical; thus hyper reactivity to stress is more or less a predictor of future hypertension. [27] Mason *et al.* proposed that because of the acute and novel nature, initially stressful psychological stimuli lose their ability to elicit significant endocrine response on re-exposure. This argument is in line with data discussed by Rose *et al.* [28] Our result is further reinforced by Caroll *et al*. who argued that increased blood pressure response to mental stress is not an independent predictor of future hypertension. According to their study, increased cardiovascular response to mental stress plays little or no causative role in hypertension. [29] Four other prospective studies have failed to confirm a positive association between physical and mental stress reactivity and later hypertension. [30,31] This further justifies the result of our study.

Isometric hand-grip test:

The cardiovascular reactivity assessed by the change in BP and heart rate after the isometric hand-grip test also showed a similar result as that of the mental arithmetic test with not much difference between the two groups and again it is not statistically significant between the two groups.

This is in close agreement with Julius *et al.* who had shown that subjects with borderline hypertension had blood pressure responses similar to those of normotensive subjects and hyper reactivity to stress was not found to be a predictor of future hypertension. [32] This is further supported by Everson *et al.* emphasising the importance of daily stress exposure in interaction with stress reactivity in prediction of cardiovascular health outcomes. [33]

In contrast, Bengt *et al.* showed that non-hypertensive men with positive family history of hypertension were characterised by increased blood pressure responses under both physical and mental stress compared to subjects with negative history of hypertension and they also suggested that such increased reactivity to different stressors could be related to subsequent development of high blood pressure in subjects prone for primary hypertension. [34] Another study conducted by Grucza R et al, in European Journal of applied physiology and occupational physiology have shown that, during sustained hand grip, heart rate and systolic blood pressure increased consistently than diastolic blood pressure in subjects at high risk for hypertension, thus as per this study it is not only the DBP changes with isometric hand-grip test but also the SBP and heart rate. [35]

Cold pressor test:

In Cold pressor test, the mean ± S.D. values of change in SBP, DBP and HR was a little more in the study group than that in the control group but its statistical significance could not be established

Our result is reinforced by Benetos *et al.* who reported that blood pressure elevation during cold-pressor test is a very common reaction in young hypertensive subjects with or without predisposition to hypertension; hence it is unlikely that this test may be used as a predictor test of future hypertension. [36] This is in contrast to Menkes *et al.*, who found a relationship only between systolic blood pressure response to cold-pressor test and later hypertension, but not for diastolic blood pressure or heart rate, while Hines et al. found hyper-reactivity based solely on diastolic blood pressure response. [9,14]

In another study, it was proposed that subjects with family history of hypertension exhibited higher basal levels of both SBP and DBP and they also exhibited higher responses to stress tests like mental arithmetic test and cold pressor test. In a study done by *Obrist and Light*, they argued that greater pressor responses are observed in response to active challenges compared to passive aversive conditions since cold-pressor test is a passive aversive challenge, it cannot be used as a predictor of future hypertension. [37] This is supported by Thomas *et al.* who in his study reported that the usefulness of cold-pressor test in predicting increased cardiovascular reactivity to stress has not been confirmed. [38]

Adrenocortical reactivity

In our study, the adrenocortical reactivity was predicted by measuring change in serum cortisol value between baseline and after the completion of all the three stress tests, the mean ± S.D. values for change in serum cortisol is significantly higher in the study group than that in the control group, implying a significant adrenocortical reactivity in the children of hypertensive parents.

This finding is in close agreement with Absi *et al.* who proposed that Cortisol responses to mental stress are greater and more persistent in persons at high risk for hypertension relative to low risk normotensives. This is because of the fact that Cortisol affects several blood pressure-related processes and regulates the expression of genes involved in blood pressure. [39] This is reinforced by Kirsch Baum *et al.* in his study which showed that Cortisol response to human CRH and mental stress can be significantly increased by hereditary factors. [40] This is in contrast with an animal study which suggests that

high adrenergic and pressor activity during acute stress occurs in some hypertension-vulnerable strains and also in some hypertension resistant strains, implying that high stress responsivity and high hypertension-susceptibility do not necessarily share a common genetic basis. [41]

Eliasson *et al.* reported that subjects with borderline or primary hypertension showed an increase in blood pressure and sympatho-adrenal response to the mental stress tests. [42] Few other studies done by Rahmouni *et al.* and Perin *et al.* suggested that sympathetic neural factors are involved in energy balance and metabolism as well as in blood pressure control, therefore adrenergic overdrive might be implicated in the development and progression of metabolic syndrome and primary hypertension. [43,44]

Our result is further reinforced by M. al ABSI *et al.* who proposed that appropriate behavioural stressors like continuous work on a pair of alternating psychological stressors leads to greater adrenocortical reactivity to stress in the hypertension prone group. This is due to greater degree of CNS activation/lower threshold for stress related reactivity. [45] And in another study, it was proposed that continuous work with different stressors like mental/physical or combined tasks produced a significant adrenocortical response in subjects at high risk for hypertension. [46]

Thus our study showed that there is increase in adrenocortical reactivity to stress tests in subjects with family history of hypertension. Moreover, this increase in adrenocortical reactivity to stress is independent of initial blood pressure levels, thus warranting a routine follow-up

CONCLUSION

Assessment of the cardiovascular reactivity showed no statistical significance after mental arithmetic test, isometric hand-grip test and cold-pressor test between the two groups. Adrenocortical reactivity assessed by change in serum Cortisol from baseline levels showed statistical significance between the two groups. Therefore we conclude that the children of hypertensive parents have increased adrenocortical reactivity to stress than does the children with no family history of hypertension

Future studies involving follow up of these subjects to find out whether this increased ACR will later on lead to hypertension can be done. Also preventive interventions like life-style modifications including stress management, diet and exercise may be warranted in those subjects with increased stress reactivity. Further studies may be done to explore the role of genes and glucocorticoid receptor sensitivity in subjects showing exaggerated reactivity (Cardiovascular and Adrenocortical) to stress. More research is needed to assess the reliability of laboratory stress tests, as compared with real-life stressors for estimating cardiovascular responsivity in an individual.

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