ORIGINAL ARTICLE

Blood Pressure Responsiveness to the Cold Pressor Test in Normotensive Young Adults

Patel Digishaben Dilipkumar[1*], Nirupma Dikshit[2], Deepak Parchwani[3]

[1]Tutor (Physiology) Dr. MK Shah Medical College and Research Centre, Ahmedabad (Gujarat)
[2]Professor (Physiology) GCS Medical College, Ahmedabad,(Gujarat)
[3]Professor (Biochemistry) GMERS Medical College, Himmatnagar,(Gujarat)

ABSTRACT

BACKGROUND: Early detection of proneness to hypertension may help an individual to lead a healthy life by altering the lifestyle. Individuals having the predisposing factors of hypertension tend to show higher and prolonged responsiveness to blood pressure following stress. With this hypothesis, in present study an attempt has been made to explore the cardiovascular reactivity to stress (cold stress) and the recovery time after the withdrawal of the stressor in normotensive young adults. **MATERIAL AND METHODS:** The study group comprised of asymptomatic normotensive participants (18-25 years) of either sex (n=50). These individuals were selected based on a positive family history of hypertension (either or both parents). The control group was comprised of similar group of individuals (n=50) but with no history of hypertension in the family. The cold pressor test was carried out. The changes in blood pressure among the participants of the hypertensive and normotensive families were compared using Student's t-test. **RESULTS:** The present study has shown that the increase in the response of the blood pressure profile is more in participants with positive family history of hypertension compared to participants with negative family history of hypertension. Recovery to the baseline after cold pressor test also was slow amongst the positive family history groups compared to participants with negative family history of hypertension. **CONCLUSION:** The present study suggests that a state of hyper-responsiveness may precede essential hypertension and that the cold pressor test could be useful as a predictor of future hypertension in a young study population. The cold pressor tests may thus identify a subgroup of individuals with an occult physiological abnormality that predisposes them to hypertension decades later.

Key words: Blood Pressure, Cold Pressor Test, Hypertension

INTRODUCTION

Hypertension (HTN) is an important worldwide public-health challenge because of its high frequency and concomitant risks of cardiovascular and kidney disease[1]. It has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life-years[2]. In India, hypertension alone is responsible for 24 % of all coronary heart disease deaths and 57 % of all the stroke deaths.[1] This is a warning sign for Indian health care system to be vigilant for adequate blood pressure management. Early detection of proneness to hypertension may enable an individual to enjoy a healthy life by altering the lifestyle. Essential hypertension is a hereditary disease and it is well documented that genes, environment, and gene-environment interactions determine an individual's blood pressure level and risk of hypertension[3]. Hypertension has been reported to be generally associated with sympathetic over-activity,[4] but the sympathetic response of certain individuals from both normotensive and hypertensive population have been reported to be more pronounced, most likely due to genetic component. Blood pressure reactivity to stress has been hypothesized to be a marker for subsequent neurogenic hypertension[5]. In evaluation of this hypothesis, studies have assessed the discriminative or prognostic value of "excessive" blood pressure reactivity to a standard cold stimulus, the Cold Pressor Test (CPT). The CPT stimulus involves both a cold and pain component, which induces a thermoregulatory reflex and global

Corresponding Author:
Patel Digishaben Dilipkumar
H/No-H-202 Parshwanath Metro city,
TP 44 Chandkheda Ahmedabad
Contact No: +919429174321
Email: digishapatel2005@yahoo.com

sympathetic activation, producing several physiological responses, including vasoconstriction and BP elevation[6,7]. Prospective studies have demonstrated that normotensive individuals with a heightened BP reactivity response to the CPT have higher ambulatory BP 3 years later, are at a 2–4-fold increased risk of developing hypertension[8-10], Even, the importance of measuring BP during recovery from the CPT has also been emphasized[11], and higher BP levels during recovery have been found to predict increases in BP levels three years later, independently of BP reactivity[12].

Reports support the notion that individuals at high risk of hypertension may have an exaggerated stress-induced cardiovascular response at a younger age and sympathetic nervous system plays a prime role in the pathogenesis of essential hypertension.

After being stimulated by a stressor, the sympathetic system triggers a rise in heart rate and blood pressure; nevertheless, heart rate and blood pressure usually tend to return to normal levels within a very short period of time after the withdrawal of the stressor[13]. Elevated blood pressure and heart rate prevail for a longer time in the susceptible individual. Naturally, the persons presenting higher cardiovascular reactivity to a stressor and slower rate of recovery after the withdrawal of the stressor causing the sympathetic stimulation may be at a high risk of developing hypertension in their future life. Despite the degree of interest shown in the subject and their prognostic implication, only recently has there been greater focus on the heritability of BP responses to CPT and the genetic correlation between BP reactivity and recovery but many questions in this field remained unanswered. A better understanding of such factors may influence the nature of therapeutic intervention in patients with or even before development of actual impairment. Keeping these things in mind, hypothesis was made in this study that autonomic response during and after cold pressor test should be more pronounced amongst individuals with a family history of hypertension. Thus, in present study an attempt has been made to explore the cardiovascular reactivity to stress (cold stress) and the recovery time after the withdrawal of the stressor in normotensive young adults i.e. this study was aimed to compare the blood pressure profile of children of hypertensives in the age group of 18-25 years with that of the age matched children of normotensives and also to identify those who are at future risk of developing hypertension.

MATERIALS AND METHODS

Study group

The study group comprised of asymptomatic normotensive participants of age group18-25 years of either sex. These individuals were selected based on a positive family history of hypertension (either or both parents). The control group was comprised of similar group of individuals (n=50) but with no history of hypertension in the family. The study protocol was approved by the Institutional Human Research Ethical Committee and informed consent was obtained (after providing a detailed study overview) from all the participants before enrolling into the study and purpose of the study was also explained to all the participants. Inclusion criteria for enrollment required that participants would be in age group of 18-25 years and were normotensive as per the JNC-7 classification[2]. However, participants with preexisting medical or psychiatric illness severe illness or any form of pharmacological intervention, impairment of speech, hearing, vision, or cognition, or any medical condition that prevented participants from adhering to the protocol and participants showing disinterest were excluded from the study.

Data collection: Participant's examination included interviews for medical (personal and family) and nutritional history. Present and past history of each case was recorded in detail regarding their general information i.e. name, age, sex, address, religion, economic status, nutritional and personal habits, education, medication and history suggestive of any systemic illness. Each participant was then examined for various anthropometric parameters

(Participants was instructed to empty their bladder prior to anthropomorphic measurement): Height (meters) was measured to the nearest 0.1 cm. Weight (Kg) was measured to the nearest 100 g. Body Mass Index (BMI) was calculated by Weight (Kg)/ height squared (m^2) [14]. Waist circumference was assessed in the standing position, midway between the highest point of the iliac crest and the lowest point of the costal margin in the midaxillary line (to the nearest 0.1 cm while the participant in standing with the abdomen relaxed, at the end of a normal expiration). Hip circumference was measured (to the nearest 0.1 cm) at the level of the femoral greater trochanter. Waist: hip ratio was then calculated from the waist and hip measures (waist circumference/hip circumference). All anthropometric measures reflect the average of 3 measurements (measured on same instrument to avoid inter-instrument variation). Age was defined as the age at the time of interview.

Sampling and Biochemical analysis: After an overnight fast of 12 hours, venous sampling was done for biochemical determinations Serum and plasma was separated by centrifugation of blood sample and were subjected for analytical procedures. Glucose (Glucose oxidase-peroxidase method, CV % : 3.4), cholesterol (Cholesterol oxidase-peroxidase method, CV % : 3.9), triglycerides (Enzymatic method, CV % : 3.6) and HDL-C (Phosphotungstic method, CV % : 4.7) were measured in fully automated analyzer.

Cold pressor test: To perform cold pressor hand test, a thick walled thermocole box measuring 38 cm X 26 cm X 18 cm, closed from all sides (by fixing its lid with the help of an adhesive), was used. A hole was made in the center of the top of the box to allow entry to one hand of the participant. Another small hole was made at the corner of the top of the box for a laboratory thermometer. Before starting the experiment the thermocole box was filled by a mixture of ice and water and laboratory thermometer was placed such that its mercury bulb immersed in mixture of ice and water. The temperature inside the box was maintained between 2^0c to 3^0c throughout the experiment.[15] Standard mercury sphygmomanometer was used to measure the blood pressure.

The study protocol consisted of first recording of resting heart rate and blood pressure: After participant had rested supine for 20 minutes, three resting blood pressure was measured in the right upper arm with a standard mercury sphygmomanometer. The recorded pressure of the three measurements was averaged. The left hand was then immersed to just above the wrist in cold water (2° to 3°C) for 1 minute and at the completion, BP and heart rate was measured and participant were asked to take out his/her hand out of the box[15]. The participant hand then was then immersed in lukewarm water for half a minute and he/she was allowed to rest. Five minute after cold pressor test, BP and heart rate were again measured. Participants were asked to refrain from ingesting beverages containing caffeine for at least 2 hour prior to test and not to exercise during 24 hour preceding test.

Statistical analysis: Statistical analysis was performed using SPSS (Statistical Package for Social Science) version 13. Descriptive statistics were done on each of the variables to obtain the frequency distributions. Quantitative variables are expressed as means ± SD. Comparisons between the positive family history groups and the normal group was analyzed by 't' tests. Analysis of variance (one way ANOVA) was used to compare subgroups. A probability value of $p < 0.05$ was considered significant

RESULTS

Table 1 shows the subgroup, anthropometric and clinical characteristics of the study participants. Among the study participants there was a preponderance of male individuals as compared with females but the gender distribution i.e. male to female ratio ($p>0.05$) as well as mean age ($p>0.05$) of two study groups were similar. A comparison of clinico-biochemical and

anthropometric characteristics revealed that there were no statically significant difference between study groups with positive family history of hypertension and negative family history of hypertension.

Table 1: Characteristics of participants.

	Participants with positive family history of HTN	Participants with negative family history of HTN
n	50	50
Male n (%)	30 (60%)	28 (56%)
BMI (Kg/m^2)	21.78 ± 3.01	21.41 ± 3.31
Waist (cm)	77.30 ± 7.89	76.07 ± 7.37
Hip(cm)	93.70 ± 6.95	91.43 ± 6.98
WHR	0.82 ± 0.05	0.83± 0.046
Fasting plasma glucose (mg/dl)	78.23 ± 8.56	76.11 ± 7.22
Triglyceride (mg/dl)	114.6 ± 14.2	116.8 ± 12.8
Total Cholesterol (mg/dl)	152.6 ± 8.4	151.1 ± 9.6
HDL-C (mg/dl)	45.8 ± 3.4	46.6 ± 3.5

Table 2: Baseline blood pressure pulse profile in male and female participants

Variables	Gender	Mean ± SD	p Value
Pulse (bpm)	Male (n:58)	82.85+11.86	0.08
	Female(n:42)	87.85+9.26	
SBP (mmHg)	Male (n:58)	119.46+8.55	0.0001
	Female(n:42)	108.76+12.29	
DBP (mmHg)	Male (n:58)	74.42+7.79	0.055
	Female(n:42)	70.24+8.74	
MAP (mmHg)	Male (n:58)	89.43+6.82	0.004
	Female(n:42)	83.07+9.16	
PP (mmHg)	Male (n:58)	45.04+9.07	0.007
	Female(n:42)	38.53+8.84	

Table 2 depicts differences of baseline blood pressure profile between male and female study population. The mean pulse rate was more amongst female participants (87.85 ±9.268) compared to male (82.85 ±11.868) however it was not significant (p=0.082). The mean SBP, MAP and Mean PP were significantly higher (p= 0.0001, 0.004 & 0.007 respectively) amongst male participants compared to female. The mean DBP was also higher in male individuals compared to female but it was not significant (p=0.055).

Table 3: Blood pressure profiles based on family history status of the participants

Variables	Family history	Mean + SD	Sig.	Sig. 2tailed
SBP (mmHg)	Positive (n:50)	113.07+12.19	0.985	0.832
	Negative (n:50)	113.73+12.01		
DBP (mmHg)	Positive (n:50)	74.27+8.95	0.159	0.043
	Negative (n:50)	69.83+7.61		
PP (mmHg)	Positive (n:50)	38.80±8.53	0.820	0.035
	Negative (n:50)	43.90±9.75		
MAP (mmHg)	Positive (n:50)	87.20±9.31	0.293	0.230
	Negative (n:50)	84.46±8.10		

Table 3 represent group statistics and analysis of data for blood pressure profile between study population based on positive and negative family history of hypertension. Comparing the data based on family history, revealed, no significant difference for SBP and MAP at basal condition (p =0.985 & 0.293 1 tailed respectively and p= 0.832 & 0.230 2 tailed respectively). DBP was more amongst individuals with positive family history and PP was more amongst individuals with negative family history however it was significant with 2 tailed only (0.043 & 0.035 respectively).

Table 4: Blood pressure profile during cold pressor test in the participants

Variables	Family history	Mean ± SD	Sig.	Sig. (2-tailed)
SBP (mmHg)	Positive (n:50)	132.60±9.96	.575	0.049
	Negative (n:50)	125.27±10.80		
DBP (mmHg)	Positive (n:50)	87.00±7.92	.426	0.040
	Negative (n:50)	82.30±9.32		
PP (mmHg)	Positive (n:50)	45.60±7.81	.151	0.774
	Negative (n:50)	42.97±9.10		
MAP (mmHg)	Positive (n:50)	102.53±7.83	.471	0.027
	Negative (n:50)	96.62±8.85		

Table 4 represent group statistics and analysis of data for blood pressure profile between study populations during cold pressor test. A significant higher values observed for SBP, DBP and MAP in positive family history individuals compared to negative family history individuals (p = 0.049, 0.40 & 0.027 respectively 2 tailed). PP was also more amongst individuals with positive family history than negative family history individuals however it was not significant (p =0.774).

When we compared the data obtained after cold pressor test for blood pressure profile between study population based on positive and negative family history of hypertension, no significant differences observed for SBP, PP and MAP (p = 0.740,0.309 & 0.751 respectively, Table 5).

Table 5: Recovery blood pressure profile after cold pressor test in the participants

Variables	Family history	Mean ± SD	p Value
SBP (mmHg)	Positive (n:50)	115.67±9.49	0.740
	Negative (n:50)	116.53±10.64	
DBP (mmHg)	Positive (n:50)	76.50±9.59	0.47
	Negative (n:50)	72.10±6.29	
PP (mmHg)	Positive (n:50)	42.17±9.12	0.309
	Negative (n:50)	44.43±7.95	
MAP (mmHg)	Positive (n:50)	87.56±8.53	0.751
	Negative (n:50)	86.91±7.08	

However DBP remains significantly elevated in participants with positive family history compared to individuals with negative family history (P = 0.47)

DISCUSSION

Hines and Brown[16] proposed that a hyper-reactive response of blood pressure to an externally applied cold stimulus was an inherited trait and that a period of vascular hyper-reactivity preceded the development of fixed hypertension. We therefore considered it worthwhile to demonstrate the usefulness of cold pressor test using a cross-sectional approach, involving normotensive children of hypertensives in the age group of 18-25 years with that of the age matched children of normotensives.

In accordance with the hypothesis, a significant independent association between blood pressure reactivity to the cold pressor test and familial history of hypertension was observed in this study i.e. a greater response was noted in participants with positive family history of hypertension than the group with negative family history of hypertension. This is in agreement with the results of previous prospective studies[17,18]. During the CPT, it was observed in this study that systolic and diastolic blood pressure increased significantly amongst participants with positive family history of hypertension. SBP increased in both groups throughout the CPT in comparison with baseline; however it was more in individuals with positive family history. With regard to DBP too the increase was observed more in participants with positive family history than control. In the present study, heart rate did not show any significant variation, this is in agreement with other studies[17,19,20]. However, few studies[21,22] are at variance with the finding of our study. Such discrepancies could be explained mainly by methodological aspects, particularly differences in duration of stimulus. In healthy human subjects, CPT triggers an increase in BP[23-25]. This may be due to an increased cardiac output during the initial period of the test with little increase in muscle sympathetic nerve activity, while an increase in this activity elevates peripheral resistance in the later period[26]. Pulse pressure also increases, mainly at the end of the test[27]. The results of the present study are in accordance with these observations (Table 2, 3, 4). The increased cardiac output is mainly due to changes in HR since SV appears unaltered[28]. The cold pressor test causes cold stress which leads to sympathetic activation and a subsequent increase in BP[29]: Stimulation of the sympathetic noradrenergic fibers causes vasoconstriction. The noradrenergic post-ganglionic sympathetic nerves also contain neuropeptide Y, a vasoconstrictor. Vasoconstrictor discharge is associated with increased arteriolar constriction and a rise in blood pressure. Impulses in nor-adrenergic sympathetic nerves beget an increase in the heart rate and the force of cardiac contraction[30,31].

Once stimulated by a stressor, the sympathetic system sets off a rise in heart rate and blood pressure, but usually these effects return to normal levels within a very short period of time (5 minutes) after the withdrawal of the stressor[13]. In persons who show higher cardiovascular reactivity to a stressor and slower rate of recovery after the withdrawal of the stressor responsible for sympathetic stimulation, the autonomic control system is not competent enough to lower heart rate and blood pressure to the baseline quickly. Naturally, this group of individuals is at high risk of an early onset of hypertension in the future.

Immersion of the right hand up to the wrist in cold water stressed the subjects through cold sensation and pain[32]. Stress exerted through the cold pressor test for a minute stimulated the sympathetic nervous system and produced an acceleration of the heart rate and rise in blood pressure, both systolic and diastolic, in comparison to those recorded before the foregoing test in all the normotensive volunteers. In the case of the offspring of the hypertensive adults, the elevation of diastolic pressure was so pronounced that the mean blood pressure increased significantly, in comparison to the baseline mean pressure. This finding corroborates the previous

finding that the children of hypertensive parents show more blood pressure responsiveness to stress[17, 18, 33].

Five minutes after the removal of the hand from the cold water, the sympathetic stimulation through cold and pain was withdrawn and blood pressure and heart rate approached the baseline level in all the volunteers from the non-hypertensive families. Nevertheless, in almost all the volunteers who parents, either or both, were reported to be hypertensive, diastolic blood pressure did not return to the normal level even 5 minutes after the withdrawal of the stimulus. Diastolic blood pressure is the index of peripheral resistance.[34] Higher diastolic pressure even 5 minutes after the withdrawal of the cold stimulus indicated that once constricted through sympathetic stimulation, vessels took longer to return to their normal original diameters in the case of those subjects. Hypertension has familial disposition. The subjects from the hypertensive families (based on the information from the volunteers, whose parents- either or both- were hypertensive) showed greater and prolonged responsiveness to sympathetic stimulation in comparison to the subjects from the non-hypertensive families, indicating the hyper- responsiveness of the sympathetic nervous system to stressor stimuli in the offspring of hypertensive adults.

This rise in blood pressure is also possibly contributed by release of some other factors like endothelin- 1, prostaglandins and angiotensin II[35,36]. As experimental studies had shown that animals develop hypertension and cardiac hypertrophy during exposure to cold. Cold exposure activates the sympathetic nervous system (SNS) which, in turn, increases the activity of the renin angiotensin system (RAS). The RAS suppresses eNOS expression and decreases nitric oxide (NO) production which contributes the development of cold induced hypertension (CIH). The RAS also mediates the cold-induced increase in endothelin – 1 (ET-1) production.

In conclusion, the present study has shown that the increase in the response of the blood pressure profile is more in participants with positive family history of hypertension compared to participants with negative family history of hypertension. Recovery to the baseline after cold pressor test also was slow amongst the positive family history groups compared to participants with negative family history of hypertension. This study may suggest a possible role of prolonged effect of stress on blood pressure in those with familial predisposition to primary hypertension and usefulness of cold pressor test in detecting individuals at high risk for developing hypertension in their future life.

Implications: CPT has been used for the diagnosis of cardiovascular reactivity in normotensive and hypertensive subjects and the response to CPT may help to identify normotensive candidates at future risk of suffering from hypertensive disease. From a public health perspective, individuals at high risk for hypertension and cardiovascular disease could be identified prior to disease development, and effective and appropriate lifestyle modifications could be implemented for primary prevention.

The present study suggests that a state of hyper-responsiveness may precede essential hypertension and that the cold pressor test could be useful as a predictor of future hypertension in a young study population. The cold pressor tests may thus identify a subgroup of individuals with an occult physiological abnormality that predisposes them to hypertension decades later. Preventive interventions may be particularly warranted in these individuals. These findings have important clinical and public health implications.

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