A Comparative Study of Cardiovascular Autonomic Functions in Stage 1 Hypertensive Subjects and Normotensive Subjects

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ABSTRACT: Worldwide essential hypertension has been responsible for 9.4 million deaths. Hypertension is major risk factor for cardiovascular complications like myocardial infarction, retinopathy, arrhythmias and sudden death. Our knowledge is still limited about the cause of increased cardiovascular risk in essential hypertension. Despite decades of research, the mechanism involved in the development of essential hypertension is still poorly understood. Autonomic nerves supplying the heart may also be involved in hypertension causing cardiac autonomic neuropathy (CAN). So the present study was undertaken to assess the cardiac autonomic functions in essential hypertensive patients as compared to normotensive subjects. We studied E: I ratio, 30:15 ratio tests for parasympathetic functions and sustained hand grip test, cold pressor test for sympathetic functions. It was found that statistically significant rise in diastolic blood pressure in hypertensive group ($p<0.05$) over normotensive group in both CPT and SHG. There was statistically significant rise in heart rate in hypertensive group ($p<0.05$) over normotensive group in E: I ratio, 30:15 ratio tests. So it can be concluded that there is definite cardiovascular autonomic dysfunction in stage 1 essential hypertensive patients as compared to normotensive subjects. There is increased sympathetic and decreased parasympathetic activity in stage 1 essential hypertension.

Keywords: Hypertension, Autonomic functions, Baroreceptor reflex function, cardiac autonomic neuropathy.

INTRODUCTION

Hypertension prevalence is approximately 26% worldwide.[1] Worldwide 80 to 95% of hypertensive subjects have essential hypertension. Essential hypertension is called as idiopathic hypertension because it is of unknown aetiology. [2] Despite decades of research, the mechanism involved in the development of essential hypertension is still poorly understood.

The sympathetic nervous system is an important regulator of circulation. Tachycardia, may be due to increased sympathetic and a decreased parasympathetic tone, leads to arrhythmias and sudden death in hypertension.[3] Emerging evidence suggests that baroreflex sensitivity for control of heart rate is reduced in hypertension which is a marker of parasympathetic functions. Thus autonomic nervous system by its sympathetic and parasympathetic divisions regulates most of the cardiovascular functions.

Hypertension may be associated with peripheral neuropathy, sensory neuropathy[4], ischemic optic neuropathy.[5] Autonomic nerves supplying the heart may also be involved in hypertension causing cardiac autonomic neuropathy (CAN).[4, 6]

Therefore the present comparative study was done to assess the cardiovascular autonomic functions in stage 1 essential hypertensive subjects according to JNC 7 and normotensive controls.

Aim and Objectives:

To measure sympathetic and parasympathetic autonomic functions in newly diagnosed stage 1 essential hypertensive subjects and compare the same in newly diagnosed essential hypertensive patients and age and gender matched healthy normotensive control.

Materials and Methods:

The study was designed as analytical, cross-sectional, comparative study in the Department of Physiology of BJGMC medical college, Pune. The synopsis of study protocol was submitted to the institutional ethics committee and approval was obtained. Study was conducted from December 2013 to September 2015. First screening was done according to inclusion-exclusion criteria.

Inclusion criteria:

For study group newly diagnosed essential hypertensive male subjects in the age group between 35 - 50 years having stage 1hypertension as per JNC 7 criteria with systolic blood pressure upto159 mm of Hg, diastolic blood pressure up to 99 mm of Hg were included. For control group healthy normotensive age, gender and body mass index (BMI) matched 50 subjects with sinus rhythm on ECG were selected.

Exclusion criteria:

For both study group and control group obese person having BMI ≥ 30 were excluded. Subjects having history of cardiac diseases, renal or endocrinal diseases, peripheral nervous system diseases, peripheral vascular disorder like Reynaud's disease, diabetes mellitus, bronchial asthma, alcohol abuse and tobacco chewing or smoking, those who regularly practice yoga or exercise training, secondary hypertension, subjects on drugs like β2 agonist, antagonist were excluded.

Procedure:

The purpose of the study and the tests to be performed on subjects were explained to them in their own language. Opportunity was given for adequate discussion and answering queries regarding the study. Written informed consent was obtained from each subject.

A detailed relevant clinical history was obtained from them. This was followed by a brief general physical examination including vital signs and complete systemic examination.

All the subjects were called in the morning hours between 10 am to 12 noon to avoid diurnal variations in autonomic functions. The subjects were instructed to avoid drinking tea and caffeine containing beverages for minimum 8 hours prior to testing. Subjects were also advised to avoid strenuous exercise for at least 24 hours before the examination. Subjects were examined in quiet room at room temperature. Heart rate responses and blood pressure responses to various manoeuvres were measured after a mandatory 30 minutes rest period.

We recorded continuous limb lead II ECG to measure resting heart rate (HR) and heart rate variability during controlled deep breathing (E:I ratio) and postural change from supine to standing (30:15 ratio). The subsequent autonomic function tests were performed only after the heart rate had returned to resting level in both normotensive and hypertensive groups.

Resting heart rate was measured in supine position with all ECG limb leads attached and resting heart rate of the subject was measured by calculating RR interval.[7]

1) 30:15 ratio: [8]

Each subject was asked to lie quietly for 3 minutes. He was then asked to stand up and remain motionless. A continuous ECG was recorded and a point was marked on ECG paper to identify the point of standing. The 30:15 ratio was calculated by measuring the R-R interval at 30th beat and at 15th beat after standing.

Calculations:[8]

30:15 ratio = RR interval at the 30th beat / RR interval at the 15th beat

- Interpretation:[9] Normal = > 1.04, Borderline= 1.01-1.03, Abnormal = <1.01

2) E: I ratio:[10]

The subject was in supine position with all ECG leads attached. A baseline recording of ECG was done for 30 sec. The patient was visually guided to breathe slowly and deeply at 6 cycles per minute. The E:I ratio was calculated from largest RR interval during expiration and smallest RR interval during inspiration. Continuous ECG record was obtained. The average value of 3 cycles was computed for each subject.

Calculation:[11]

E: I ratio = Longest RR interval during deep expiration /Shortest RR interval during deep inspiration

Interpretation:[9] Normal = > 1.21, Borderline= 1.11-1.20, Abnormal = <1.10

3) Sustained hand grip test (SHG):[12]

Recording of Maximum Voluntary Contraction (MVC):

The subjects were asked to produce a maximum effort by their dominant hand squeezing the bars of hand grip dynamometer as hard as possible and maintaining the maximal effort for 2-3 sec and maximum voluntary contraction (MVC) was recorded. Three trials were allowed with a brief pause of 10 sec between each trial to avoid excessive fatigue.

MVC is defined as the maximum force generated by the subject during the three attempts using the hand grip dynamometer.

Recording of BP at 30% of MVC:

The subject was asked to apply pressure on a handgrip dynamometer for 1 minute at 30% of maximal voluntary contraction and simultaneously the blood pressure changes were observed by using automatic digital machine. The difference between the diastolic blood pressure records (DBP) just before the release of contraction and just before startinghandgrip manoeuvre, was taken as a measure of the response.

Interpretation:[9] **(**Normal: ≥16 mmHg rise in DBP, Borderline: 11-15 mmHg rise in DBP, Abnormal: ≤10 mmHg rise in DBP)

4) Cold Pressor Test (CPT): [13]

Resting blood pressure was recorded with the subject sitting comfortably following which his hand is immersed in cold water upto wrist and the temperature was maintained at 4-6^{0}C throughout the procedure. Blood pressure measurement was made from the other arm at 30 second intervals for a period of 2 minutes. After 2 minutes, the subject was asked to remove his hand. The maximum rise in the diastolic pressure was recorded. Participants were instructed to maintain normal breathing patterns and avoid breath holding or performance of valsalva manoeuvre.

Interpretation: [9] Normal: > 16 mmHg rise in DBP**,** Borderline: 11-15 mmHg rise in DBP**,** Abnormal: <10 mmHg rise in DBP.

Statistical Analysis:

The results were given as Mean ± Standard deviation. Comparisons were performed using z-test for two group comparisons. A p-value of less than 0.05 was considered as statistically significant and p-value of less than 0.001 was considered statistically highly significant. Statistical software namely SPSS (Statistical Package for the Social Science) version 20 was used for the analysis of data. Microsoft word and Microsoft excel have been used to create text documents, graphs and tables etc.

RESULTS

Table no. 1: Demographic profile among hypertensive and normotensive groups.

Parameters	Hypertensive (n=50)		Normotensive (n=50)		z value	p value
	Mean	SD	Mean	SD		
Age (Years)	44.06	3.413	44.70	3.157	0.97	>0.05
BMI (kg/m^2)	24.93	1.760	24.87	2.280	0.14	>0.05
p values <0.05 : statistically significant*, p values <0.0001: statistically highly significant**, p values >0.05 : not significant						

Table no. 2: Comparison of parasympathetic autonomic functions between hypertensive and normotensive groups.

Parameters	Hypertensive (n=50)		Normotensive (n=50)		z value	p value
	Mean	SD	Mean	SD		
E:I ratio	1.06	0.085	1.2316	0.052	12.34	<0.0001**
30:15 ratio	1.00	0.072	1.10	0.052	7.36	<0.0001**
p values <0.05 : statistically significant*, p values <0.0001: statistically highly significant**, p values >0.05 : not significant						

Table no.3: Comparison of sympathetic autonomic functions between hypertensive and normotensive groups.

Parameters	Hypertensive (n=50)		Normotensive (n=50)		z value	p value
	Mean	SD	Mean	SD		
ΔDBP SHG (mmHg)	18.78	2.636	17.74	2.230	2.13	<0.05*
ΔDBP CPT (mmHg)	16.92	2.137	12.56	2.233	9.98	<0.0001**
p-values <0.05 : statistically significant*, p values <0.0001: statistically highly significant**, p values >0.05 : not significant.						

4. DISCUSSION

1) Cold pressor test (CPT):

CPT stimulates adrenergic receptors of sympathetic nervous system increasing peripheral vasoconstriction leading to increased blood pressure.[14] The afferent limb of the reflex pathway is by somatic fibers whereas the efferent pathway is by sympathetic fibers.[15] In our study the increase in blood pressure and heart rate response was significantly more in stage 1 essential hypertensive subjects than normotensive subjects during cold pressor test ($p<0.05$). It suggests that there may be increased sympathetic activity in stage 1 essential hypertensive group than normotensive group. [16]

2) Sustained hand grip: During sustained hand grip also the increase in blood pressure and heart rate response was significantly more in stage 1 essential hypertensive subjects than normotensive subjects.

There is increase in metabolites like lactic acid and adenosine which are detected by metabolic sensitive nerve endings within the skeletal muscle interstitium. These substances increase the discharge of group IV (metaborecetors) afferent fibers and initiate a potent reflex increasing sympathetic nerve activity. This leads to vasoconstriction which increases blood pressure.[5] Recruitment of new motor units to maintain muscle tension expands the excitation of the central nervous system. Thus the voluntary activity increases the excitatory state of the central nervous system and results in a possible increase in sympathetic outflow, leading to increased blood pressure.[6] Due to muscle fatigue there is increased voluntary effort to produce a certain force which stimulates central nervous system. As a result of this central nervous system stimulation, sympathetic activity increases leading to an increased heart rate and blood pressure. [6]

3) E: I test: In the present study we got statistically significantly lower mean value of E: I ratio in stage 1 essential hypertensive group as compared to normotensive group ($p < 0.0001$**). In hypertensive individuals, there is no increase in heart rate during inspiration because of loss of beat to beat variation. So ECG finding was longer R-R interval as compared to healthy individuals during phase of inspiration. So E:I ratio was reduced in hypertensive individuals may be due to baroreceptor desensitization.

4) 30:15 ratio: In the present study hypertensive subjects had decreased 30:15 ratio. Hypertensive subjects showed no significant increase in heart rate immediately after standing may be due to decreased baroreceptor sensitivity. Hypertensive subjects showed no significant increase in heart rate immediately after standing may be due to decreased baroreceptor sensitivity. When normal healthy subject assumes an erect posture from supine position, gravity causes pooling of blood in the lower limbs. As a result venous return, cardiac output and arterial blood pressure decreases. This leads to decreased stretch of baroreceptors causing activation of vasomotor center, which leads to increased sympathetic discharge, decreased vagal tone and an instantaneous increase in heart rate. On standing the heart rate increases until it reaches a maximum at about the 15th beat, after which it slows down to a stable state at about 30th beat due to baroreflex.[10] This reflex phenomenon to standing is due to unloading of the baroreceptors. This decreased blood pressure decreases the firing of baroreceptor impulses to nucleus tractus solitarius unloading it from inhibitory influence of baroreceptors on nucleus tractus solitarius.[15]

Causes for decreased baroreceptor sensitivity may be[3]-

1. Decreased vascular elasticity and endothelial damage because of atherosclerosis and aging.
2. Alterations in the release of various factors from endothelium.
3. Enhanced circulating renin, angiotensin II and action of circulating angiotensin II on brain (area postrema and nucleus tractus solitarius).

Autonomic dysregulation in stage 1 essential hypertension may be due to some abnormalities either in-

1. Brainstem control centers of autonomic nervous system –

All major autonomic effector responses are mediated through neurons that release rapidly acting neurotransmitters like glutamate. Other interneurons release slow transmitters like monoamines and various peptides. Each slow transmitter modulates the responsiveness of the fast transmitter pathways. In essential hypertension, repeated increase in dopamine neuron activity strengthens synaptic transmission of the hypothalamic defence pathway. This lowers the threshold for eliciting the sympatho-adrenal changes responsible for the chronic elevation of blood pressure. [17]

2. Afferent pathways which modify the response of central controllers by feedback mechanism like baroreceptors and chemoreceptors-In hypertension there is a chronic increase in cardiopulmonary load, which gives rise to vagal deficit. [17]
3. There may be cardiac autonomic neuropathy in hypertensive subjects like peripheral neuropathy in diabetes, leading to myelin degeneration and axonal degeneration due to hypoxia, chronic inflammation, oxidative stress, free radical damage to autonomic nerves.[4]
4. A defect in neuronal uptake of norepinephrine, by exposing adrenergic receptors to high local norepinephrine concentration, may be important in the pathogenesis of blood pressure elevation in some patients with essential hypertension.[18]
5. Essential hypertension can be caused by strong stimulation of the sympathetic nervous system during states of anxiety and stress. There is excitation of the hypothalamus by different types of stress. [19]

CONCLUSION: From all above results in our study, we conclude that increased sympathetic activity and decreased parasympathetic activity in stage 1 essential hypertensive group as compared to normotensive group.

There was no any conflict of interest.

Application of the study:

1. It will also help clinically treating the hypertensive patients.
2. If any abnormality is detected in parasympathetic autonomic functions in early stage of hypertension, future complications can be prevented.
3. People with cardiac autonomic neuropathy can undergo yoga and lifestyle modification to prevent further damage and complications.

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