Original article:

Modulation of Autonomic dysfunctions in Hypertensive patients taking Beta-blockers

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Abstract:

Introduction: Hypertension is a "silent killer" has multi-factorial underlying defect. A number of physiological derangements are involved in elevation of blood pressure. Along with excessive salt intake, obesity and dyslipidemia autonomic dysfunctions too take part in this. Present study was conducted to study autonomic disturbances in hypertensive subjects and role of beta blockers in their alleviation and possible sustenance.

Material & Methods: Present study was conducted on 25 non-diabetic early hypertensive subjects of 1-2 years duration and who were put on single drug therapy (Beta Blockers) and their autonomic functions were tested before and after taking drug and also results were compared with age and sex matched 25 normotensive controls.

Results: Results showed mean value of pulse rate was lowest in group HT (66.56±12.13) which is statistically significant when compared to group NT (77.78±5.55) while Systolic & Diastolic BP was at significantly higher value. Sympathetic functions tests in study group were significantly predominant while Parasympathetic functions were low and non-significant. This shows study group subjects were having higher mean values of sympathetic functions tests.

Conclusion: There is an increased sympathetic activity in the hypertensive individuals in comparison to normotensive subjects. The hypertensive patients receiving beta-blockers showed maximum depression of sympathetic activity when it is compared with normotensive subjects. There is no change in parasympathetic activity of hypertensive groups in comparison to normotensive subjects.

Key words: Hypertension, Beta Blockers, Autonomic dysfunctions, autonomic function tests

Introduction:

Primary or essential Hypertension is common ageing problem. It is usually asymptomatic readily detectable but not so easily treatable malady [1]. Untreated or badly treated hypertension causes a number of serious disorders. When the resistance against which the left ventricle pump is elevated for a long period due to high blood pressure, there is cardiac muscle hypertrophy. Left ventricular hypertrophy is associated with poor prognosis. The total oxygen consumption of the heart, already increased by work of expelling blood against a raised pressure is increased further because there is more muscle. Therefore, any decrease in coronary blood flow has more serious consequences in hypertensive patients than in normal individuals[2]. Hypertension is a complex disease where the high blood pressure is only one of the numerous coronary risk factors. The incidence of atherosclerosis too increases in hypertension and myocardial infarcts are common

even when the heart is not enlarged[3][4]. The ability to compensate for the high peripheral resistance is exceeded eventually and the heart fails. The hypertensive individuals are also predisposed to thrombosis of cerebral vessels and cerebral hemorrhage[5]. Renal failure is another complication of hypertension.

The overactive Renin-angiotensin-aldosterone system (RAAS) plays an important part in many pathologic conditions including hypertension, heart failure, and renal disease[6]. However, the incidence of heart failure, strokes and renal failure can be markedly reduced by active treatment of hypertension, even when the hypertension is relatively mild. Lifestyle modification is an important part of management of hypertension along with antihypertensive drugs.

The sympathetic nervous system is an important regulator of circulation. Its activity is increased in hypertension and heart failure and adversely affects prognosis[7]. Sympathetic overactivity in hypertension, independent of the blood pressure, may be conducive to premature atherosclerosis by inducing insulin resistance and dyslipidemia[8]. Sympathetic over activity through its trophic effect on blood vessels causing vascular smooth muscle hypertrophy potentiate vasoconstriction[9]. This, in turn, accelerates hypertension and the metabolic syndrome. The hypertrophy of small coronary arterioles decreases the coronary reserve and enhances coronary spasms. Tachycardia, which is due to increase sympathetic tone and a decrease parasympathetic tone, favors arrhythmias and sudden death in congestive heart failure and hypertension[10]. Judicious use of appropriate drug is very important to further improve the efficacy of antihypertensive treatment in those patients who in addition to high blood pressure, also have other associated risk factors. The various classes of antihypertensive drugs act differently in relation to autonomic nerves system activity.

In a study done to evaluate in the hypertensive patients the cardiovascular and sympathetic response to exercise after long term beta-adrenergic blockade (Atenolol), it was observed that heart rate and blood pressure were lower at rest and throughout the exercise in treated patients. [13]It was concluded that long term administration of beta adrenergic blockers increased myocardial re-polarization time and reduces sympathetic nervous system activity. The prevalence of autonomic imbalance found in hypertensive subjects can be assessed by various cardiovascular automatic function tests[11]. These tests have been divided to asses parasympathetic and sympathetic activities separately. Resting heart rate, resting blood pressure, cold pressor test and hand grip test are the measures of sympathetic nervous system activity. While standing/lying ratio, 30:15 ration, valsalva ration and tachycardia ration are the tests for evaluation of parasympathetic nervous system activity.

Various studies have been carried out to study the changes in automatic nervous system activity on hypertensive patients having different drug regime worldwide with variable inferences. Material & Methods:

Present study was conducted on 25 non-diabetic early hypertensive subjects of 1-2 years duration and who were put on single drug therapy (Beta Blockers) which were grouped as Hypertensive group (HT). Their autonomic functions were tested before and after taking drug. Results were compared with age and sex matched 25 normotensive controls.

The examination of autonomic nervous system has been carried out in the following manner:

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Heart rate,

Respiratory rate,

Pulse and temperature

Area of excessive sweating or anhydrosis.

Autonomic functions tests

The various autonomic function tests were carried out with the help of Cardiart-108T/MK-VI ECG machine (BPL make) using standard limb lead II. But for Galvanic Skin Resistance Polyrite-4 Medicare Machine was used. Polyrite recorder is a highly sensitive oscillography capable of simultaneously recording signals in the different modes from many sources.

The various autonomic function tests carried out were:

1. Standing to Lying Ration (S/L Ratio)
2. 30:15 ratio
3. Valsalva ratio
4. Tachycardia ratio
5. Galvanic skin resistance (GSR)
6. Hand grip test (HGT)
7. Cold pressor test (CPT)

Observations and Results:

TABLE I -PRE-TEST MEAN VALUES OF PULSE RATE AND BLOOD PRESSURE IN THE SIX GROUPS

Parameter	**Group I (NT) Mean ± SD**	**Group II (HT) Mean ± SD**	***p-value***	**Significance**
Pulse rate (per min)	77.78±5.55	66.56±12.13	<0.05*	Significant
SBP (mm Hg)	130.1±6.98	143.36±21.68	<0.05*	Significant
DBP (mm Hg)	75.92 ±5.67	87±9.13	<0.05*	Significant

Table I shows significant* higher mean values of Pulse Rate, Systolic Blood Pressure and Diastolic Blood pressure in case of HT (Hypertensive) group as compared to NT (Normotensive) group.

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TABLE II

COMPARATIVE STUDY OF SYMPATHETIC FUNCTIONS IN TWO GROUPS (N=50)

Parameter	Group I (NT) mean±SD	Group II (HT) mean±SD	p-value	Significance
CPT				
Rise in SBP (mmHg)	11.84±4.75	7.04±3.65	<0.05*	Significant
Rise in DBP (mmHg)	8.24±4.90	3.36±3.90	<0.05*	Significant
HGT				
Rise in SBP (mmHg)	12.08±6.23	4.88±5.74	<0.05*	Significant
Rise in DBP (mmHg)	13.60±6.97	5.12±6.00	<0.05*	Significant
GSR	158.00±4.80	170.00±8.60	<0.05*	Significant

Table II shows significant higher mean values ($p<0.05$) of Cold Pressure test (CPT), Hand grip Test (HGT) and Galvanic Skin Response (GSR) in case of HT (Hypertensive) group as compared to NT (Normotensive) group.

TABLE III

COMPARATIVE STUDY OF PARASYMPATHETIC FUNCTION TESTS IN SIX GROUPS (N-50)

Parameter	Group I (N) mean ± SD	Group II mean ± SD	p-value	Significance
S/L ratio	1.13±028	1.05±0.15	>0.05	Non-significant
30-15 ratio	1.05±0.16	1.01±0.05	>0.05	Non-significant
Valsalva ratio	1.36±0.27	1.26±0.09	>0.05	Non-significant
Tachycardia ratio	0.87±0.10	0.90±0.09	>0.05	Non-significant

Discussion:

The present study showed that mean value of pulse rate in hypertensive group HT was (66.56±12.13) when compared to group NT (77.78±5.55). The heart rate variability is statistically significant ($p<0.05$) among group I (HT) when intergroup comparison is done. The significant fall in heart rate in patients taking beta-blockers (group II) could be due to depression of beta-1 adrenergic receptors present in sinoaortic node. When stimulated they increase heart rate causing positive chronotropic effect and also cause increased ventricular contractility with positive ionotropic effect. There depression causes negative effect. This results in decreased sympathetic discharge. These results are consistent with earlier studies done on persons taking betablockers confirming that beta blockers reduce heart rate[12] [13].

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Table I shows that pretest mean value for systolic blood pressure is statistically higher in group HT (143.36±21.68) when compared to normotensive subjects group (NT) (130.1±1.98) ($p<0.05$). This indicates a comparatively higher degree of sympathetic tone in all patients of hypertension despite various antihypertensive treatments.

The spontaneously occurring changes in central haemodynamics have been followed in young males with essential hypertension over a 17-year period. There was found a gradual increase in total peripheral resistance and blood pressure, and a gradual fall in cardiac output and stroke volume[14].

The pretest mean value for diastolic blood pressure group showed significant variation in diastolic blood pressure (83.54±10.14) in hypertensive group (HT) when compared to normotensive group (NT) (75.92±5.67) The values are statistically significant ($p<0.05$). This observation again indicates a relatively significant raised diastolic blood pressure in hypertensive groups as compared to normotensive group.

This could be explained again due to sustained increase in sympathetic activity in patients of hypertension in spite of antihypertensive treatment. Since most current evidence suggests that, in humans, sustained increase in heart rate are basically due to decreased parasympathetic tone. These findings support the concept that autonomic imbalance contributes to the pathogenesis of hypertension. In addition since diastolic blood pressure relates more closely to vascular resistance than to cardiac function, these results also suggest that increased sympathetic tone may increase diastolic blood pressure by causing vascular smooth-muscle cell proliferation and vascular remodeling[15].

There are basically two fundamental haemodynamic changes in an established case of hypertension. There is an increased total peripheral resistance and subnormal blood flow particularly during exercise or activity. Antihypertensive drugs which act on central and peripheral adrenergic receptors cause regaining of normal vascular resistance, cardiac output, and thus blood pressure[16].

Data reveals that rise in systolic blood pressure in response to stress induced by CPT is less in group II (7.04±3.65), as compared to normotensive group I (N) (11.84±4.75). These results are statistically significant ($p.<0.05$). Table II also shows that magnitude of rise of diastolic blood pressure in response to CPT is less in group II (3.36±3.90) when compared to normotensive subjects group I (N) (8.24±4.90). This value too is significant statistically ($p<0.05$). Also there is significant fall in rise of diastolic blood pressure in response to HGT in group HT (5.12±6.00), group when compared to normotensive subjects group I (N) (13.60±6.97). Values are significant ($p<0.05$). In case of galvanic skin resistance (GSR) the hypertensive group HT showed mean values of (170±8.6) showed significant variation ($p<0.05$) in comparison to normotensive subjects (158±4.80).

These finding indicate that Beta blocking drugs suppress sympathetic activity consequently resulting in less increase in systolic as well as diastolic blood pressure in response to CPT in patients of hypertension on drugs regime which include beta blockers ruse of systolic as well as diastolic blood pressure in response to CPT.

Beta blockers having strong intrinsic sympatholytic activity which reduce heart rate and cardiac output, but due to a reflex increase in total peripheral resistance index, blood pressure is

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unchanged or only slightly reduced[17]. With long term use total peripheral resistance drops towards pretreatment level and pressure falls. During exercise heart rate and cardiac output are reduced, but less with conventional beta blockers and resistance is unchanged or slightly reduced [18].

Immediate as well as long term reduction in blood pressure can be produced by alpha-adrenergic receptor blockers (prazosin, doxazosin, trimazosin), and in these cases the fall occurs via reduction in total peripheral resistance index without reflex tachycardia. These drugs also increase exercise stroke volume and cardiac output with long term treatment. The antihypertensive action of beta-receptor blockers has largely remain unknown yet appears mainly due to the reduction of cardiac output. Combined alpha-beta-adrenergic blockade lowers blood pressure predominantly by alpha-adrenoceptor-mediated reduction of systemic vascular resistance both when induced acutely and during long-term administration[19].

Table III depicts the results obtained after performing various parasympathetic function tests on subjects of both groups.

Data revealed that there is no significant change in S/L ratio hypertensive group HT (1.05±0.15) when compared to normotensive subjects group I (NT) (1.13±0.28). The mean value for 30:15 ration in hypertensive group HT(1.03±0.21) show statistically insignificant changes when compared to normotensive group (NT) (1.05±0.16) ($p>0.05$). Intergroup comparison of the hypertensive patients on different drug regime also show insignificant variation 30:15 ration among themselves.

The mean value for valsalva ration in group HT (1.26±0.19 show statistically insignificant ($p>0.05$) variation when compared to normotensive group (1.36±0.27). Even intergroup comparison of the hypertensive patients on different drug regime show no remarkable variation among themselves in valsalva ratio.

The mean value for techycardia ratio again showed statistically insignificant variation ($p>0.05$) in group HT (0.90±0.09), compared to normotensive subjects group (NT) (0.87±0.10). The intergroup comparison in techycardia ratio also shows insignificant variation ($p>0.05$).

Thus, these tests on parasympathetic activity (S/L ratio, 30:15 ration, valsalva ration, tachycardia ration) in hypertensive groups HT and normotensive group (NT) show statistically insignificant variations. The overall present study in hypertensive patients have shown that there is an increased sympathetic activity in all the hypertensive patients with no alteration in parasympathetic activity when intergroup subjects were compared.

Greater sympathetic drive has been established in the early stages of essential hypertension, suggesting that neuro-hormonal dys-regulation may be key to its etiology the progression of hypertension and subsequent end-organ damage, such as raised arterial stiffness and left ventricular hypertrophy [20].

The sympathetic and parasympathetic nervous systems are not “opposites”; rather, the interactions are complex.A dynamic interaction occurs between them; these interactions are modulated partially by secondary messengers (cAMP and cGMP). The parasympathetic nervous system can inhibit sympathetic nerve traffic presynaptically. Likewise, sympathetic activation can inhibit parasympathetic activation presynaptically[21].

Summary and Conclusions:

The hypertensive patients receiving beta-blockers show maximum depression of sympathetic activity

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when it is compared with other antihypertensive groups on different drug regime and against normotensive subjects.

There is no change in parasympathetic activity of hypertensive groups in comparison to normotensive subjects.

Abbreviations: CPT: Cold pressor test; HGT: hand Grip test; GSR: Galvanic skin resistance; SBP: Systolic blood pressure; DBP; Diastolic blood pressure

Ethical Considerations: Ethical considerations were given due regard in this study. Patients and subjects were asked to volunteer for test by signing proper Performa. They were told about the pain and distress they would undergo while performing tests.

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