

# Association of Sympathovagal Imbalance with Cognitive Deficit, Insulin Resistance and Oxidative Stress in Newly Diagnosed Hypertension

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## ABSTRACT

**Background and Aim:** Hypertension has been reported to be caused by sympathovagal imbalance and is associated with a wide variety of cognitive loss. The aim of present study is to study the association of sympathovagal imbalance with cognitive deficit, insulin resistance and oxidative stress in newly diagnosed hypertensive subjects. **Methods:** 84 subjects (42 normotensives and 42 hypertensives) aged between 18-44 years were included in this case-control study. The demographic, anthropometric, basal parameters, heart rate variability (HRV), cardiovascular autonomic function tests (CAFTs), event-related potential P300 and biochemical parameters were recorded. Association of various factors with cognitive deficit was studied by Pearson correlation analysis and independent contribution of factors to cognitive deficit was assessed by multiple regression analysis. **Results:** LF-HF ratio was increased and total power of HRV was reduced in hypertensives. Among CAFTs, 30:15 ratio and DDBP<sub>1HG</sub> group were increased; E: I ratio was decreased in hypertensive group. The latency of P300 was significantly prolonged in hypertensives and P300 latency was positively correlated and linked with LF: HF ratio (the marker of SVI) in hypertensives. The fasting blood glucose, insulin, HOMA-IR, hsCRP and total oxidant capacity were increased and antioxidant status was decreased in hypertensive groups. **Conclusion:** Newly diagnosed hypertensive subjects have sympathovagal imbalance and considerable memory impairment even before medical intervention. Insulin resistance and oxidative stress contribute to the memory impairment and sympathovagal imbalance could be the physiological link for cognitive loss in newly diagnosed hypertensive subjects.

**Key words:** Newly diagnosed hypertension, Sympathovagal imbalance, Cognitive deficit, Insulin resistance, Oxidative stress.

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## INTRODUCTION

According to 7<sup>th</sup> Joint National Committee (JNC-7) criteria, hypertension is defined as systolic blood pressure  $\geq 140$  mmHg and diastolic blood pressure  $\geq 90$  mmHg.<sup>[1]</sup> Globally, more than one billion adults above 25 years of age have hypertension which may rise to 1.56 billion by 2025.<sup>[2,3]</sup> In developing countries like India, hypertension is the cause for 57% of all deaths from stroke and 24% of all deaths from coronary heart disease.<sup>[4]</sup> High systolic blood pressure contributes to ischemic stroke and lacunar infarct, diffuse white matter damage or leukoaraiosis and this reduction in white-matter density possibly causes impaired cognitive functioning especially of executive functions.<sup>[5]</sup> Hypertension, an established risk factor for cognitive deficit accounts for the third cause of death, out of one in eight deaths worldwide.<sup>[6,7]</sup> Cognitive deficit is defined as an average cognitive performance at around the thirty-fifth to forty-fifth percentiles of normative data affecting one or multiple domains of cognition, though the cut-off to detect cognitive deficit is at fifth to tenth percentile.<sup>[8]</sup>

Though there are various sophisticated techniques for determining cognitive impairment, recently the event related potential recorded in the form of positive wave at 300ms (P300) has been considered as a better tool for assessing cognitive deficit. P300 is closely related to cognition-related brain functions like attention, intelligence and working memory as P300 activates multiple brain cortical areas which include frontal, prefrontal and parietal region.<sup>[9-13]</sup> Autonomic homeostasis contributes to higher brain functions including cognition.<sup>[14]</sup>

Recently we have reported from our laboratory that sympathovagal imbalance (SVI) caused by vagal inhibition in addition to the heightened sympathetic activity as the physiological basis of hypertension.<sup>[15,16]</sup> Further, metabolic derangements which include dyslipidemia, insulin resistance and retrograde inflammation are contributors to sympathovagal imbalance in hypertension.<sup>[17,18]</sup> However, there is paucity of data demonstrating the association of autonomic imbalance and metabolic derangements

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with cognitive impairment in newly diagnosed hypertensive subjects in Indian population. Also, in previous studies assessing memory impairment in hypertension, cognitive functions have been assessed subjectively in hypertension and not objectively. Therefore, the present study was designed to assess the association of sympathovagal imbalance, insulin resistance and oxidative stress with cognitive deficit in patients with hypertension.

## METHODS

This case-control study was conducted after receiving approval from the JIPMER Scientific Advisory Committee and Institute Ethics Committee for human studies. This study was conducted in the Autonomic Function Testing Laboratory and Electrophysiology Laboratory, Department of Physiology, JIPMER. The subjects were recruited from medicine outpatient department of JIPMER.

### Sample size calculation

Total sample size was calculated to be 84 subjects (42 control subjects and 42 hypertensive subjects). The objective of this study was to measure and compare the LF-HF ratio with P300. Therefore, using previous reference, considering the mean and standard deviation values of LF-HF ratio, accepting power as 80% and keeping the level of significance 5%,<sup>[19]</sup> the total sample size calculated by Open Epi software was 84.

### Estimation of biochemical parameters

Written informed consent was obtained from all the subjects prior to commencement of the study. From each subject, 5 ml of fasting blood sample was collected and fasting blood glucose was estimated by oxidation – reduction method using glucometer (Accu-chek Performa, Roche diagnostics; Sweden). The serum insulin was assayed using ELISA kit from Chemux BioScience Inc, CA and HOMA-IR is computed from the formula,  $\text{HOMA-IR} = \text{fasting serum insulin } (\mu\text{U/ml}) \times \text{fasting blood glucose (mg/dl)} / 405$ . The inflammatory marker hsCRP was assayed using ELISA kit from Calbiotech Inc., CA, oxidative stress markers was assayed using QuantiChrom™ TBARS assay kit from bioassay systems, CA to detect oxidant status and QuantiChrom™ Antioxidant assay kit from bioassay systems, CA to detect antioxidant status.

### I. Inclusion criteria:

Based on Joint National Committee -7 classification (1) the subjects were divided into:

Normotensives (n=42): systolic blood pressure 100-119 mmHg and diastolic blood pressure 60-79 mmHg, healthy person.

Hypertensives (n=42): Newly diagnosed hypertensives, having systolic blood pressure of 140 mmHg or above and diastolic blood pressure of 90 mmHg or above.

### II. Exclusion criteria:

1. Subjects receiving any medications or having any acute illness.
2. History of smoking, alcoholism, endocrinal disorder, cardiovascular disease, neurological disorders and renal disorders.
3. Subjects practicing regular sports / athletic activities.

### Recording of blood pressure

Subjects were asked to report to autonomic function laboratory of Physiology Department at about 9 AM following a light breakfast, without tea or coffee. After obtaining the informed consent, their age, height, body weight and body mass index (BMI) were recorded. Omron (SEM 1 Model), the automatic BP monitor (Omron Healthcare Co. Ltd, Kyoto, Japan) was used to measure BP. The cuff size of the equipment was

121 mm (width) × 446 mm (length) and cuff tube length was 600 mm. The subjects were asked to sit upright with back straight on a wooden armed chair and instructed to rest one forearm on a wooden table comfortably. They were asked to rest their other forearm on the hand rest of the chair. The height of the table was adjusted to an extent; the middle of the arm of the subjects when placed on the table coincided with the level of the heart. The blood pressure cuff was tied on the arm approximately 2 cm above the cubital fossa and care was taken that the cuff was neither too tight nor loose. For each participant, systolic blood pressure, diastolic blood pressure, heart rate were recorded at an interval of 5 mins in each arm twice and the mean of the 4 recordings was considered for each parameter.

### Recording of heart rate variability (HRV)

After 15 mins of supine rest, ECG was recorded for 5 mins for short-term HRV analysis following the guidelines of Task Force.<sup>[20]</sup> ECG electrodes were connected and Lead II ECG was acquired at 500 samples per second for each channel using PowerLab 8/30 ML 870 data acquisition system with Lab chart pro software. The acquired 5 min resting lead II ECG (filtered with band pass filters) was carefully analyzed for ectopic and artifacts, which were meticulously removed manually. The detection of R-waves was done with a thresholding algorithm of Lab chart pro software. From the RR tachogram, power spectral analysis was performed by fast-fourier transform. Time-domain parameters (RMSSD, SDNN, NN50 and pNN50) and frequency domain parameters [total power (TP) of HRV, normalized LF power (LFnu), normalized HF power (HFnu), ratio of low-frequency to high-frequency power (LF-HF ratio)] were computed using HRV analysis software (Kubios HRV, version 2.2 Finland).

### Recording of P300 event-related potential

Cognitive event-related potential (P300, positive wave at 300ms) was recorded in electrophysiology laboratory of Department of Physiology, JIPMER using Nihon Kohden Electrophysiology / electromyography (EP/EMG) machine. The recommendation of the International Federation of Clinical Neurophysiology was used<sup>[21]</sup> and as per protocol of recording in Indian laboratory set-up.<sup>[22]</sup> The subjects were instructed to come with cleaned oil-free scalp (shampoo head bath) and without ear wax before recording. They were asked to relax for 10 mins and the procedure of recording was explained to them in detail. The scalp of the subject was cleaned with spirit and the electrode placements were done according to the 10-20 international system of EEG. The active, reference and ground electrodes were connected to channel 1 preamplifier with an impedance of  $\leq 2 \text{ k}\Omega$ . The midpoint between both the tragus and the midpoint between nasion and occipital protuberance were marked. At the point of intersection of above midpoints active recording electrode Cz (central zero point on scalp) was placed. With the help of jumper electrode, reference electrodes were placed one on the two mastoids. The ground electrode was placed in forehead Fz near to the hairline. The electrodes used were made of Ag-AgCl. P300 was recorded in the context of a standard auditory oddball paradigm. The band pass filter range was kept at 0.1 Hz and 50 Hz. The auditory stimulus was given binaurally through a headphone. The subjects were asked to relax totally and asked to concentrate on the rare stimulus. The stimuli were given with the intensity of 40 dB with the 'tone' as the target or rare stimulus and 'click' as non-target or frequent stimulus. The stimulus frequency for tone burst and click were 2000 Hz and 1000 Hz respectively. The click duration was kept at 0.1 ms. The stimulus occurrence speed was 1 stimulus per second. Only investigator and the subject were present in the laboratory and total silence was ensured during the recording. The participants were asked to open their eyes and fix to a point to avoid alpha waves in EEG. The rare stimuli were applied randomly and the percentage of rare stimuli was set at 20% and

frequent stimuli at 80% of random. The stimulation rate was 0.5 Hz per second. The number of stimuli to be given was preset at 30. The signals were picked by electrodes, filtered, amplified, averaged, displayed and analyzed using Neuropack software on the screen of Nihon Khoden EP/EMG machine.

N1 was the negative wave at 100 ms, N2 was the negative wave at 200 ms, P2 was the positive wave at 200 ms and P3 was the positive wave at 300 ms. Among these waves, P300 i.e., the positive wave at 300ms, was considered as the marker of cognition. The procedure of recording was repeated for reproducibility of P300 and the marking was done for the latencies of N1, P2, N2 and P300 in milliseconds and the amplitudes of N1-P2, P2-N2 and N2-P3 in microvolts.

### Statistical analysis of data

Statistical analysis was performed by SPSS version 19 (SPSS; SPSS Inc., Chicago, IL) for Windows. The data were subjected to Kolmogorov-Smirnov normality test. All the data were expressed as mean  $\pm$  SD. The intergroup differences in mean between the controls, prehypertensives and hypertensives were compared using one-way ANOVA and posthoc analysis was done using Tukey-Kramer for normally distributed data. The association of P300 with cardiovascular and biochemical parameters was assessed by Pearson's correlation analysis. Multiple regression analysis was performed to assess the independent association of P300 with different variables in hypertensives after adjusting for BMI and gender.

## RESULTS

No significant difference was observed in age ( $P=0.1007$ ) in control and hypertensive group (Table 1). BMI and heart rate were significantly increased in hypertensives compared to controls (Table 1). On analysis of the frequency domain and time domain parameters of short term HRV, TP was significantly reduced among the hypertensives ( $P<0.0001$ ) compared to the controls. When the absolute powers were expressed in normalized units, LFnu was significantly elevated and HFnu was depressed in hypertensives ( $P<0.0001$ ) when compared to controls. The LF-HF ratio was significantly elevated in hypertensives ( $P<0.0001$ ) compared to controls (Table 1). The analysis of the time domain parameters revealed that there was a highly significant decrease in RMSSD ( $P<0.0001$ ) and SDNN ( $P<0.0001$ ) among hypertensives compared to controls. pNN50 ( $P<0.0001$ ) and NN50 ( $P<0.0001$ ) were significantly reduced in hypertensive group compared to controls (Table 1).

There was a significant reduction in E: I ratio ( $P<0.005$ ) and a significant increase in 30:15 ratio ( $P<0.0001$ ) and  $\Delta\text{DBP}_{\text{IHG}}$  during isometric hand-grip in hypertensive group compared to control group. The P300 latency was significantly prolonged in hypertensives compared to controls (Table 2). Though the amplitude of P300 wave is decreased in hypertensive subjects the difference was not statistically significant. Hypertensives showed significantly elevated fasting blood sugar ( $P=0.0004$ ), insulin ( $P<0.0001$ ) and HOMA-IR ( $P<0.0001$ ) values compared to controls (Table 3). There was significant elevation of hsCRP and TBARS in hypertensive group compared to control group. The total antioxidant status was reduced in hypertensive group compared to controls.

Table 4 depicts the correlation of P300 with various important parameters like BMI, fasting blood sugar, Insulin, HOMA-IR, TBARS, hsCRP and LF-HF ratio of control and hypertensive groups. There was significant positive correlation with hypertensive group when compared to control group. Table 5 shows multiple regression analysis to assess the independent association of P300 (as dependent variable) with BMI, HOMA-IR, TBARS, hsCRP and LF-HF ratio (as independent variables) in hypertensive group. In the present study, there is significant independent contribution of HOMA-IR ( $\beta=0.245$ ,  $P=0.040$ ), TBARS ( $\beta=0.266$ ,  $P=0.032$ ), LF-HF ratio ( $\beta=0.351$ ,  $P=0.009$ ).

**Table 1: Comparison of demographic, anthropometric, basal parameters, frequency domain indices (FDI) and time domain indices (TDI) of heart rate variability (HRV) and cardiac autonomic function tests (CAFT) parameters between control and hypertensive groups.**

Parameters	Controls (n=42)	Hypertensives (n=42)	P value
Age (years)	30.19 $\pm$ 5.01	32.21 $\pm$ 6.09	0.1007
Body weight (kg)	64.12 $\pm$ 10.68	71.82 $\pm$ 6.27	0.0001
Height (m)	1.62 $\pm$ 0.10	1.64 $\pm$ 0.09	0.3382
BMI (Kg/m <sup>2</sup> )	24.34 $\pm$ 2.81	26.86 $\pm$ 2.59	0.0001
BHR (bpm)	73.24 $\pm$ 10.58	85.21 $\pm$ 9.70	0.0001
SBP (mmHg)	111.88 $\pm$ 7.98	149.50 $\pm$ 8.11	0.0001
DBP (mmHg)	68.48 $\pm$ 6.19	99.31 $\pm$ 6.48	0.0001
FDI parameters			
TP(ms <sup>2</sup> )	1054.64 $\pm$ 734.05	553.55 $\pm$ 300.51	0.0001
LFnu	40.54 $\pm$ 16.27	63.07 $\pm$ 12.07	0.0001
HFnu	59.46 $\pm$ 17.13	36.92 $\pm$ 2.07	0.0001
LF-HF ratio	0.82 $\pm$ 0.54	1.99 $\pm$ 0.96	0.0001
TDI parameters			
SDNN (ms)	46.20 $\pm$ 19.61	24.06 $\pm$ 8.04	0.0001
RMSSD (ms)	64.53 $\pm$ 24.67	29.05 $\pm$ 12.13	0.0001
NN50	50.35 $\pm$ 21.08	29.83 $\pm$ 12.45	0.0001
pNN50 (%)	30.83 $\pm$ 13.65	17.04 $\pm$ 5.84	0.0001
CAFT Parameters			
30:15 ratio	1.21 $\pm$ 0.29	1.50 $\pm$ 0.35	0.0001
E:I ratio	1.39 $\pm$ 0.17	1.22 $\pm$ 0.35	0.0058
DDBP <sub>IHG</sub>	19.30 $\pm$ 5.22	28.19 $\pm$ 6.45	0.0001

Values expressed as mean  $\pm$  SD; Analysis done by student's unpaired *t* test.

The P values less than 0.05 were considered statistically significant.

BMI: Body Mass Index; BHR: Basal heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TP: Total Power; LFnu: Low Frequency component expressed as normalized unit; HFnu: High Frequency component expressed as normalized unit; LF-HF ratio: ratio of low-frequency power to high-frequency power of heart rate variability; SDNN: Standard Deviation of Normal to Normal interval; RMSSD: Square root of the mean squared differences of successive normal to normal intervals; NN50: the number of interval differences of successive NN intervals greater than 50 ms; pNN50: the proportion derived by dividing NN50 by the total number of NN intervals; 30:15 ratio: Ratio between maximum RR interval at 30<sup>th</sup> beat and minimum RR interval at 15<sup>th</sup> beat; E:I ratio: ratio of longest RR interval during expiration to the shortest RR interval during inspiration averaged over 6 cycles of respiration;  $\Delta\text{DBP}_{\text{IHG}}$ : difference in diastolic blood pressure between supine and Isometric Hand Grip

## DISCUSSION

In the present study, a significant prolongation of P300 latency in treatment naïve hypertensives (Table 2) indicates significant memory impairment in these subjects, as event-related potential is an established marker of higher cognitive function. Hypertension has been reported to be associated with a broad variety of cognitive loss including attention deficit, slowing of mental processing speed, impaired memory and reduced abstract reasoning.<sup>[23-27]</sup> However, there are no reports from Indian subcontinent assessing the mechanisms of or the factors contributing to the cognitive loss in hypertension.

Previous studies have reported that the primary pathophysiology involved in elevated blood pressure in hypertensive subjects is the sympathovagal



**Table 2: Comparison of P300 latency and amplitude between control and hypertensive groups.**

Parameters	Controls (n=42)	Hypertensives (n=42)	P value
N100 (ms)	107.71 ± 11.77	121.07 ± 31.40	0.0116
P200 (ms)	194.95 ± 26.62	204.90 ± 28.25	0.1005
N200(ms)	231.76 ± 25.70	246.12 ± 31.67	0.0251
P300 (ms)	341.57 ± 44.56	366.40 ± 30.53	0.0038
N <sub>1</sub> -P <sub>2</sub> μv	8.07 ± 5.75	5.65 ± 3.81	0.0256
P <sub>2</sub> -N <sub>2</sub> μv	3.60 ± 2.42	3.04 ± 2.67	0.3168
N <sub>2</sub> -P <sub>3</sub> μv	12.03 ± 4.92	10.98 ± 2.57	0.2237

Values expressed as mean ± SD; Analysis done by student's unpaired *t* test.

The P values less than 0.05 were considered statistically significant.

N100 (N1): Negative wave that appears in 100ms from application of stimulus in ERP tracing. P200 (P2): Positive wave that appears in 200ms from application of stimulus in ERP tracing. N200 (N2): Negative wave that appears in 200ms from application of stimulus in ERP tracing. P300 (P3): Positive wave that appears in 300ms from application of stimulus in ERP tracing.

**Table 3: Comparison of biochemical parameters between control and hypertensive groups.**

Parameters	Controls (n=42)	Hypertensives (n=42)	P value
FBG (mg/dl)	79.09 ± 9.59	86.29 ± 8.32	0.0004
Insulin (μU/l)	7.48 ± 2.98	21.40 ± 4.63	0.0001
HOMA IR	1.47 ± 0.63	4.34 ± 3.29	0.0001
hsCRP (mmol/l)	2.24 ± 1.92	11.81 ± 6.42	0.0001
TBARS (μM)	1.03 ± 0.73	2.29 ± 1.06	0.0001
TAS (μM)	419.23 ± 130.68	250.85 ± 85.63	0.0001

Values expressed as mean ± SD; Analysis done by student's unpaired *t* test.

The P values less than 0.05 were considered statistically significant.

FBG: Fasting blood glucose, HOMA- IR: Homeostasis model assessment of insulin resistance;

hsCRP: high-sensitivity C-reactive protein; TBARS: Thiobarbituric acid reactive substance; TAS: Total oxidant status.

imbalance.<sup>[16,17]</sup> In the present study, LF-HF ratio, the indicator of sympathovagal imbalance,<sup>[28]</sup> was significantly elevated in hypertensive groups (Table 1), indicating the presence of sympathovagal imbalance in treatment naïve hypertensives. The LF-HF ratio was significantly correlated with P300 in hypertensive groups, but not in control groups (Table 4), depicting the significant association of sympathovagal imbalance with cognitive impairment in hypertensives. Further, LF-HF ratio had independent contribution to P300 in hypertensives as demonstrated by multiple regression analysis (Table 5). Thus, findings of the present study indicate the close link of sympathovagal imbalance with memory loss in hypertensive subjects.

All the time-domain indices of HRV (RMSSD, SDNN, NN50, pNN50) were significantly reduced in hypertensive groups compared to control group (Table 1) demonstrating that parasympathetic autonomic modulation was considerably less in these subjects as time-domain indices indicate cardiac vagal drive.<sup>[20,28]</sup> Further, this was supplemented by reduced HFnu and TP of HRV (Table 1). As HFnu of HRV is the indicator of vagal drive to the heart and TP reflects overall power of vagal cardiac regulation.<sup>[29]</sup> Thus, these findings represent decreased vagal drive of cardiac autonomic control in hypertensive subjects. Significant raise

**Table 4: Correlation of P300 with various important parameters of control and hypertensive groups.**

Parameters	Controls (n=42)		Hypertensives (n=42)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
BMI	0.092	0.148	0.315	0.009
FPG	0.032	0.256	0.268	0.044
Plasma insulin	0.076	0.190	0.287	0.032
HOMA-IR	0.040	0.282	0.380	0.007
TBARS	0.030	0.257	0.298	0.013
hsCRP	0.080	0.162	0.260	0.046
LF-HF ratio	0.160	0.117	0.438	0.000

The p value <0.05 was considered significant. P300: Positive wave at 300 ms in event-related potential tracing; BMI: Body mass index; RPP: Rate pressure product; LF-HF ratio: ratio of low frequency to high frequency power of heart rate variability.

in 30:15 ratio and fall in E: I ratio in hypertensives (Table 1) indicates diminution in parasympathetic reactivity in these subjects, as these two parameters represent vagal reactivity. Significant increase in  $\Delta\text{DBP}_{\text{IHG}}$  in hypertensives indicates increased sympathetic reactivity in these subjects, as  $\Delta\text{DBP}_{\text{IHG}}$  represents sympathetic reactivity.<sup>[30]</sup> Thus, autonomic imbalance in subjects with hypertension is due to the augmented sympathetic activity as well as reactivity and diminished vagal activity as well as reactivity.

There are reports of metabolic derangements in hypertension.<sup>[16]</sup> There is also report of decline in cognitive function in conditions of metabolic derangements like dyslipidemia, IR and oxidative stress.<sup>[31-33]</sup> However, there are no reports demonstrating cognitive impairment in hypertensives, especially in Indian population. In the present study, fasting blood sugar, insulin and HOMA-IR were significantly increased in hypertensives compared to normotensives (Table 3). Persistent hyperglycemia, advanced glycation end-products (AGEs) and hyperinsulinemia have been implicated in the genesis of memory loss, brain aging and Alzheimer's disease.<sup>[31,32]</sup> Insulin resistance has also been strongly implicated in the development of cognitive impairment in Alzheimer's disease.<sup>[33]</sup> In the present study, levels of fasting blood glucose, insulin and HOMA-IR were not only significantly high in hypertensive patients compared to control subjects (Table 3), but also HOMA-IR was significantly correlated with P300 in these subjects (Table 4). Further, HOMA-IR had independent contribution to P300 in hypertensives as demonstrated by multiple regression analysis (Table 5). Fasting blood glucose and insulin were not included in the same regression model to avoid multicollinearity. Thus, it appears that hyperinsulinemia and insulin resistance are closely linked to cognitive impairment in hypertensive patients. Recently we have reported the link of insulin resistance to sympathovagal imbalance in polycystic ovary syndrome and prehypertension and in salt-preferring individuals and first-degree relatives of diabetes patients. Also, in the present study, HOMA-IR was significantly correlated with LF-HF ratio in hypertensive group. Therefore, sympathovagal imbalance might be the pathophysiological link between IR and cognitive impairment in hypertension.

Another linking mechanism of cognitive impairment in hypertensive patients could be the oxidative stress, as level of TBARS was significantly increased in hypertensive group compared to control groups (Table 3), Further, TBARS was significantly correlated with P300 in hypertensive group (Table 4) and TBARS had significant independent contribution to P300 in hypertensives (Table 5). Hippocampal oxidative stress has been implicated in the cognitive deficit in experimental diabetes model in

**Table 5: Multiple regression analysis to assess the independent association of P300 (as dependable variable) with various parameters (as independent variables) in hypertensive group after adjusting for BMI and gender.**

Independent variables	Standardized regression coefficient beta	95% confidence interval		P Values
		Upper limit	Lower limit	
BMI (Kg/m <sup>2</sup> )	0.178	0.007	0.292	0.108
HOMA-IR	0.245	0.003	1.380	0.040
TBARS	0.266	0.004	1.602	0.032
hsCRP	0.145	0.009	0.168	0.142
LF-HF ratio	0.351	0.017	2.275	0.009

The p value <0.05 was considered significant. P300: Positive wave at 300 ms in event-related potential tracing; BMI: Body mass index; LF-HF ratio: ratio of low-frequency to high-frequency power of heart rate variability.

mice. Therefore, oxidative stress could be a plausible mechanism of cognitive impairment in hypertensive patients too as fasting blood glucose was also significantly more in these patients. Recently, oxidative stress has been linked to autonomic imbalance and we have reported the association of oxidative stress with sympathovagal imbalance in hypertension.<sup>[19]</sup> Further, in the present study, TBARS was significantly correlated with LF-HF ratio in hypertensive group (Table 4). Also, total anti-oxidant status was considerably reduced in hypertensives. Therefore, it appears that the sympathovagal imbalance could be the pathophysiological link between oxidative stress and cognitive deficit in hypertensive patients. Though hsCRP, the nonspecific marker of inflammation was significantly more in hypertensives, it was not correlated with P300 in these subjects. Therefore, retrograde inflammation is unlikely to contribute to the memory loss in these subjects.

In the present study, high BMI in hypertensive group could be suggested as a potential cause of memory impairment, as obesity has been observed to be associated with memory loss.<sup>[29,34]</sup> Though BMI was significantly correlated with P300 in hypertensive group (Table 4), the independent contribution of BMI to P300 was not significant (Table 5). Thus, it is unlikely that high BMI would have contributed to memory loss in hypertensive patients. Moreover, there is also report that association of cognitive impairment with BMI is not significant.<sup>[35]</sup>

Though the exact cause of cognitive loss is not known, few reports have suggested that cognitive decline in hypertension could be due to cerebrovascular damage.<sup>[36]</sup> The connection of the frontal lobes to other cortical and subcortical structures such as limbic system is disrupted in white matter tract injuries that have profound influence on autonomic functions.<sup>[14]</sup> However, the role of autonomic dysfunction affecting cognition has not been studied in hypertension.

As hypertension is known to cause cerebrovascular disease,<sup>[37]</sup> and reports indicate the role of brain infarction and white matter disease in cognitive impairment,<sup>[38,39]</sup> cerebrovascular mechanisms have been proposed for cognitive impairment in hypertensives. Among the non-cerebrovascular mechanisms, hyperinsulinemia, insulin resistance, oxidative stress and deposition of AGEs and amyloid  $\beta$  proteins in the brain substance have been proposed as the mechanisms of cognitive deficit in diabetes.<sup>[40,41]</sup> Further, as practice of yoga has been reported to improve cerebral blood flow<sup>[42]</sup> and restore sympathovagal balance,<sup>[43]</sup> role of yoga in the improvement of cognitive functions in hypertensive patients should also be investigated.

The novelty of the present study is that this is the first report linking sympathovagal imbalance with cognitive deficit in treatment naïve

hypertensives from Indian subcontinent. This is also the first report from Indian subcontinent assessing the contribution of insulin resistance and oxidative stress to cognitive impairment and the association of IR and oxidative stress with sympathovagal imbalance in hypertensive patients before initiation of treatment. The findings of the present study demonstrate that even before the hypertension was diagnosed clinically, these patients have considerable memory impairment. As such in developing countries like India where detection of hypertension can occur late and compliance to treatment is not very effective, cognitive loss in patients suffering from chronic disease like hypertension, especially in younger population could pose serious threat to socioeconomic development.

### Limitations of the Study

Though the limitations of the present study are that we have not estimated amyloid  $\beta$  proteins and not done brain imaging investigations in hypertensive patients, sympathovagal imbalance could be the physiological basis of cognitive impairment in hypertensives as chronic sympathovagal imbalance with sympathetic accentuation has been reported to cause hypertrophy of vascular wall with narrowing of vessel lumen causing decreased cerebral perfusion that might contribute to the cerebrovascular component of cognitive impairment.<sup>[41]</sup> In the present study there is not a single hypertensive subject that does not appear to have metabolic alterations and therefore, a group of non-metabolic disease patients should have been included to eliminate the impact of metabolic alterations on cognitive deficit, which is a major limitation of the study. Further, other measures of cognitive assessment such as memory function tests through questionnaires should have been included in the study protocol.

### CONCLUSION

Newly diagnosed hypertensive subjects have sympathovagal imbalance and considerable memory impairment even before medical intervention. Insulin resistance and oxidative stress contribute to the memory impairment and sympathovagal imbalance could be the physiological link for cognitive loss in newly diagnosed hypertensive subjects.

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There is no acknowledgement in this study.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

### ABBREVIATIONS USED

**FBG:** Fasting blood glucose; **HOMA- IR:** Homeostasis model assessment of insulin resistance; **hsCRP:** high-sensitivity C-reactive protein; **TBARS:** Thiobarbituric acid reactive substance; **TAS:** Total oxidant status.

### SUMMARY

Hypertension has been reported to be caused by sympathovagal imbalance and is associated with a wide variety of cognitive loss. The aim of present study is to study the association of sympathovagal imbalance with cognitive deficit, insulin resistance and oxidative stress in newly diagnosed hypertensive subjects. Eighty four subjects (42 normotensives and 42 hypertensives) aged between 18-44 years were included in this case-control study. The demographic, anthropometric, basal parameters, heart rate variability (HRV), cardiovascular autonomic function tests (CAFTs), event-related potential P300 and biochemical parameters were recorded. Association of various factors with cognitive deficit was studied by Pearson correlation analysis and independent contribution

of factors to cognitive deficit was assessed by multiple regression analysis. LF-HF ratio was increased and total power of HRV was reduced in hypertensives. Among CAFTs, 30:15 ratio and DDBPIHG group were increased; E: I ratio was decreased in hypertensive group. The latency of P300 was significantly prolonged in hypertensives and P300 latency was positively correlated and linked with LF: HF ratio (the marker of SVI) in hypertensives. The fasting blood glucose, insulin, HOMA-IR, hsCRP and total oxidant capacity were increased and antioxidant status was decreased in hypertensive groups. Newly diagnosed hypertensive subjects have sympathovagal imbalance and considerable memory impairment even before medical intervention. Insulin resistance and oxidative stress contribute to the memory impairment and sympathovagal imbalance could be the physiological link for cognitive loss in newly diagnosed hypertensive subjects.

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