Am J Neurodegener Dis 2021;10(4):38-49
www.AJND.us /ISSN:2165-591X/AJND0133782

Original Article

Link of neurocognitive deficit to impaired cardiovagal modulation in prehypertensives is comparable to newly diagnosed hypertensives in young Indian population

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Received March 31, 2021; Accepted June 28, 2021; Epub August 15, 2021; Published August 30, 2021

Abstract: Background: Hypertension has been reported to cause impaired cardiovagal modulation and a wide variety of cognitive loss. However, the link cardiovagal modulation to neurocognitive impairment has not been studied yet. The present study has compared the link cardiovagal modulation to neurocognitive impairment between prehypertension and newly diagnosed hypertension in young adults. Methods: One hundred forty-seven subjects (42 normotensives, 54 prehypertensives and 51 newly diagnosed 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 in all the groups. Association of various parameters with neurocognitive deficit was studied by Pearson correlation analysis and independent contribution of various factors to cognitive deficit was assessed by multiple regression analysis in the study groups. Results: Total power (TP) of HRV, the marker of cardiovagal modulation was reduced in both prehypertensives and hypertensives compared to controls. Among CAFTs, the ΔDBP_{IHG} was increased, and 30:15 ratio and E:I ratio were decreased in both study groups. The latency of P300 (the marker of neurocognition) was significantly prolonged in prehypertensives and hypertensives and P300 latency was significantly associated with reduction in TP in both the groups. HOMA-IR was increased, and total oxidant capacity was decreased in prehypertensives and hypertensives, and both these parameters had independent contribution to P300. Conclusion: Prehypertensives had considerable autonomic imbalance, reduced cardiovagal modulation and neurocognitive deficit that were comparable to newly diagnosed hypertensives. Though the causal relationship between cardiovagal modulation and neurocognitive impairment can't be established from the findings of the present study, it appears that neurocognitive deficit might have some possible link to the decreased cardiovagal modulation and metabolic derangements in young prehypertensives and hypertensives.

Keywords: Prehypertension, newly diagnosed hypertension, cardiovagal modulation, neurocognitive deficit, metabolic derangements

Introduction

According to 7th Joint National Committee (JNC-7) criteria, prehypertension is defined as SBP 120-139 mmHg and DBP 80-89 mmHg, and hypertension is defined as SBP ≥140 mmHg and DBP ≥90 mmHg [1]. Globally, more than one billion adults above 25 years of age have hypertension, which may rise to 1.56 billion by 2025 [2, 3]. In developing countries like India, hypertension is the cause for 24% of deaths from coronary heart disease (CHD) and 57% of all deaths due to stroke [4]. The report of a multicentric study has indicated the presence of higher neurocognitive loss in hypertensive patients compared to the neurocognitive impairment observed in the general population [5]. Many epidemiological studies reveal that hypertension precedes the cognitive impairment, and small vessel disease causing vascular brain damage is the major risk factor for cognitive loss [6]. Due to vascular injury, the lesions in subcortical white matter in hypertension may interrupt the neuronal circuits of prefrontal cortex-basal ganglia, which in turn causes impairment of the cognitive domain especially of the

executive functions [7, 8]. Further, vascular pathology and neurodegenerative lesions have been observed to coexist in most dementias [9].

It has been documented that the high systolic blood pressure (SBP) contributes to lacunar infarct and diffuse white matter damage (leukoaraiosis), and the consequent reduction in white-matter density is proposed to be the cause of impaired cognitive functioning, especially of the executive functions in age-related dementia [10]. Hypertension, an established risk factor for cognitive deficit accounts for the third cause of death, out of one in eight deaths worldwide [10, 11]. Before developing hypertension, a person remains in the state of prehypertension for many years. Although hypertension is an established risk to cause deficit in cognitive function, the prehypertension as a risk factor for cognitive impairment has not been studied yet. We have reported the association of decreased level of cognition with autonomic imbalance and cardiovascular risks in prehypertension [12].

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 [13]. Though there are various sophisticated techniques for determining cognitive impairment, recently the event related potential recorded in the form of positive wave at 300 milliseconds (P300) has been considered a better tool for the assessment of cognitive deficit [14]. It has been reported that brain functions like intelligence, attention, and working memory are closely related to P300, as P300 is the expression of activities of multiple brain cortical areas that include frontal, prefrontal and parietal regions [15]. Though neurocognitive deficit in hypertension has recently been reported in a multicentric study [5], the cognitive status in this study was assessed by using questionnaires of Minimal Cognitive Examination (MCE) scale, which does not quantitatively assess the central neurocognitive functions. Also in this study, the average age of the subjects was 60 years. In another recent study, through cognitive impairment in hypertension was assessed in relatively younger population, the Mini-Mental State Examination (MMSE) was used for the assessment of cognitive function [16]. Thus, quantitative and accurate techniques such as estimation of P300 have not been used in the previous works for neurocognitive assessments in hypertension and the studies have not been conducted in younger population.

State of autonomic balance is reported to influence higher brain functions including cognition [17]. Recently we have reported from our laboratory that sympathovagal imbalance (SVI) caused by parasympathetic inhibition along with heightened sympathetic tone as the physiological basis of development prehypertension and hypertension [18]. Further, metabolic derangements which include dyslipidemia, retrograde inflammation and insulin resistance (IR) have been demonstrated to contribute to SVI in hypertension [19, 20]. We have also reported the possible association of autonomic imbalance and metabolic derangements with cognitive impairment in hypertension [21]. However, the pathophysiology of cognitive impairment in prehypertension and hypertension and its link to autonomic and cardiometabolic derangements in these conditions have not been studied yet. Prehypertension is more commonly observed in younger individuals, which persists silently for a longer time before clinically manifesting as hypertension. Nevertheless, the pathophysiological mechanisms of cognitive impairment in prehypertension and hypertension in younger age group have not been assessed yet. Hence, in the present study, we have evaluated the difference in the level of neurocognitive impairment and its plausible pathophysiologic mechanisms in younger prehypertensives and hypertensives in Indian population.

Methods

This case-control study was conducted after receiving approval from the Scientific Advisory Committee and Institute Ethics Committee for Human Studies (No. JIP/IEC/2015/8/408) of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. The study was conducted in the Autonomic Function Testing (AFT) Laboratory and Electrophysiology Laboratory, Department of Physiology, JIPMER. The subjects were recruited from medicine out-patient department of JIPMER hospital.

Sample size calculation

The estimated toot sample size was 147 (42 normotensives, 54 prehypertensives and 51 newly diagnosed hypertensives). The objective of this study was to measure and compare the link of cardiovagal modulation expressed as total power (TP) of heart rate variability (HRV) with P300. Therefore, using previous reference, considering the mean and standard deviation values of TP, accepting power as 80% and keeping the level of significance 5% [21], the total sample size calculated by Open Epi software was 84.

Inclusion criteria

The subjects were divided into: Normotensives (n=42): Healthy subjects having SBP 100-119 mmHg and diastolic blood pressure (DBP) 60-79 mmHg, healthy person.

Prehypertensives (n=54): Apparently healthy subjects having SBP 120-139 mmHg and DBP 80-89 mmHg.

Hypertensives (n=51): Newly diagnosed hypertensives, having SBP of 140 mmHg or above and DBP of 90 mmHg or above, before initiation of antihypertensive treatment.

The subjects in the age group of 20 to 40 years, having body mass index (BMI) between 21 to 30, non-smokers, non-alcoholics, and subjects not receiving any kind of medications, were included in the three groups.

Exclusion criteria

1. Subjects having any acute or chronic illness.

2. History of endocrinal disorders including diabetes, CVD, neurological disorders and renal disorders.

3. Subjects practicing regular sports or athletic activities.

Recording of anthropometric parameters and blood pressure

Instructions were given to the subjects to come to Physiology Department at about 9 AM following a light breakfast without tea or coffee and report to AFT laboratory. Prior to commencement of the study, written informed consent was obtained from all the subjects. 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. For each participant, SBP, DBP, BHR were recorded at an interval of five minutes in each arm twice and the mean of the four recordings was considered for each parameter. Rate pressure product (RPP) was calculated from BP and HR values.

Recording of short-term HRV

Subject was asked to lie down for 15 minutes in supine position on a couch. For short-term HRV analysis, the ECG was recorded continuously for 5 minutes following the methodology as described earlier and the guidelines of Task Force for HRV measurement [22, 23]. After connecting the ECG electrodes, Lead II ECG was acquired at a speed of 500 samples per second for each channel using PowerLab 8/30 ML 870 data acquisition system with Lab chart pro software. Power spectral analysis was performed from the RR tachogram. Time-domain parameters (RMSSD, SDNN, NN50 and pNN50) and parameters of frequency domain of HRV such as total power (TP), normalized LF power (LFnu), normalized HF power (HFnu), ratio of low-frequency to high-frequency power (LF-HF ratio) were calculated with the help of HRV analysis software (Kubios HRV, version 2.2 Finland).

Conventional autonomic function tests (CAFTs)

The following CAFTs were performed as per the standard procedures [24].

HR and BP response to standing: In the supine position, first BP and ECG were recorded. The subject was asked to make the standing posture in 3 seconds from the supine posture. During the procedure, ECG was recorded continuously. Using an automatic BP monitor (Omron, SEM-1, Kyoto, Japan), BP was recorded every 40 seconds till fifth minute. The 30:15 ratio (ratio of maximum RR interval at thirtieth beat to minimum RR interval at fifteenth beat after standing) was calculated.

HR response to deep breathing: The subject being in sitting posture, monitoring of respiration and HR was done from stethographic respi-

ratory tracings recorded on the multichannel polygraph (Nihon-Kohden, Tokyo, Japan) and electrocardiographic recording, respectively. ECG and respiration tracings were taken for 30 seconds as baseline recording. Instruction was given to the subject to take slow and deep inhalation and then exhale in a slow and deep manner such the duration of each breathing cycle is about 10 seconds, which comprises of 6 breathing cycles/min. From electrocardiographic tracing, E/I ratio was calculated as the ratio of average RR interval during exhalation to average RR interval during inhalation in 6 cycles of deep breathing.

BP response to isometric handgrip: The baseline BP was recorded. The subject was instructed to press handgrip dynamometer at 30% of maximum voluntary contraction for 2 minutes. Recording of BP was done at the first and second minutes of contraction. ΔDBP_{IHG} was calculated as maximum rise in DBP above baseline.

Recording of P300 event-related potential

Cognitive event-related potential (P300, positive wave at 300 ms) was recorded in electrophysiology laboratory of Department of Physiology, JIPMER using Nihon Kohden Electrophysiology/electromyography (EP/EMG) machine. The International Federation of Clinical Neurophysiology recommendation was used [25], and as per protocol of recording in Indian laboratory set-up [12]. 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 minutes, 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 ≤2 kΩ. 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 be completely relaxed and instructed to concentrate on the rare stimulus. The stimulus intensity was 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. In the laboratory, only investigator and the subject were present 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 300 ms, 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.

Estimation of biochemical parameters

From each subject, five ml of fasting blood sample was collected, and fasting blood glucose (FBG) 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, HOMA-IR = fasting serum insulin (μU/ml) × fasting blood glucose (mg/dl)/405. The inflammatory marker hsCRP was assayed using ELISA kit from Calbiotech Inc.,

Table 1. Comparison of age, BMI, basal parameters, frequency & time domain indices of HRV, and CAFT parameters between normotensive (n=42), prehypertensive (n=54) and hypertensive (n=51) groups

Parameter	Normotensives (A)	Prehypertensives (B)	Hypertensives (C)	P-1 A vs. B	P-2 A vs. C	P-3 B vs. C	Group P
Age (years)	30.19±5.01	29.46±5.88	31.85±6.22	0.81	0.35	0.08	0.1007
BMI (Kg/m^2)	24.34±2.81	25.12±3.34	26.80±2.52	0.3998	0.0003	0.0106	0.0003
BHR (bpm)	73.24±10.58	78.89±8.10	84.20±9.10	0.0094	<0.0001	0.0102	<0.0001
SBP (mmHg)	111.88±7.98	132.10±5.80	149.24±8.16	<0.0001	<0.0001	<0.0001	<0.0001
DBP (mmHg)	68.48±6.19	85.17±2.92	99.58±6.23	<0.0001	<0.0001	<0.0001	<0.0001
RPP (mmHg/min)	81.96±13.57	101.20±10.85	127.11±12.20	<0.0001	<0.0001	<0.0001	<0.0001
HRV Parameters							
TP (ms^2)	1054.64±534.05	728.22±245.20	550.50±202.46	<0.0001	<0.0001	0.0239	<0.0001
LFnu	40.54±16.27	57.80±18.90	64.50±19.27	<0.0001	<0.0001	0.1504	<0.0001
HFnu	59.46±17.13	42.20±15.92	35.50±12.15	<0.0001	<0.0001	0.0630	<0.0001
LF-HF ratio	0.82±0.54	1.37±0.80	1.86±0.91	0.0022	<0.0001	0.0044	<0.0001
SDNN (ms)	46.20±19.61	30.15±9.88	24.02±8.56	<0.0001	<0.0001	0.0630	<0.0001
RMSSD (ms)	64.53±24.67	38.78±20.10	28.12±10.12	<0.0001	<0.0001	0.0124	<0.0001
NN50	50.35±21.08	37.25±12.30	28.80±12.40	0.0002	<0.0001	0.0151	<0.0001
pNN50 (%)	30.83±13.65	23.56±8.10	17.50±5.81	0.0008	<0.0001	0.0036	<0.0001
CAFT Parameters							
30:15 ratio	1.21±0.29	1.18±0.20	1.10±0.12	0.7652	0.0335	0.1258	0.0312
E:I ratio	1.39±0.17	1.32±0.35	1.20±0.30	0.4730	0.0059	0.0907	0.0069
ΔDBP_{IHG}	19.30±5.22	24.80±6.40	28.24±6.40	<0.0001	<0.0001	0.0122	<0.0001

Values expressed as mean ± SD; Analysis done by one way ANOVA. P-1: The *P* values between normotensives and prehypertensives. P-2: The *P* values between normotensives and hypertensives. P-3: The *P* values between prehypertensives and hypertensives. Group P: The *P* values of overall three groups. BMI: Body Mass Index; HRV: Heart rate variability; BHR: Basal heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RPP: Rate pressure product; 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; Mean RR: Mean RR interval; 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 30th beat and minimum RR interval at 15th beat; CAFT: Conventional autonomic function tests; E:I ratio: ratio of longest RR interval during expiration to the shortest RR interval during inspiration averaged over 6 cycles of respiration; ΔDBP_{IHG}: difference in diastolic blood pressure between supine and Isometric Hand Grip.

CA, oxidative stress markers were assayed using Quanti-Chrom-TM TBARS assay kit from bioassay systems, CA to detect oxidant status and Quanti-Chrom-TM Antioxidant assay kit from bioassay systems, CA to detect antioxidant status.

Statistical analysis of data

Using SPSS version 19 (SPSS; SPSS Inc., Chicago, IL) for Windows, statistical analysis was carried out. To check for normality, Kolmogorov-Smirnov normality test was used. All the data were expressed as mean ± SD. For normally distributed data, the intergroup differences in mean between the controls, prehypertensives and hypertensives were compared using one-way ANOVA and post-hoc analysis was done using Tukey-Krammer test. The association of P300 with cardiovascular and biochemical parameters was assessed by Pearson's correlation analysis. To assess the independent association of P300 with different variables in prehypertensives and hypertensives after adjusting for BMI and gender, multiple regression analysis was performed.

Results

Age was not significantly different between the subjects of three groups (**Table 1**). Though the BMI was not significantly more in prehypertensives compared to normotensives, it was significantly high in hypertensives (P=0.0003).

Table 2. Comparison of P300 latency and amplitude between normotensive (n=42), prehypertensive (n=54) and hypertensive (n=51) groups

Parameter	Normotensives (A)	Prehypertensives (B)	Hypertensives (C)	P-1 A vs. B	P-2 A vs. C	P-3 B vs. C	Group P
P300 Latency							
N_{100} (ms)	107.71±11.77	117.80±18.56	123.35±27.42	0.0495	0.0011	0.3567	0.0017
P_{200} (ms)	194.95±26.62	201.90±30.56	205.92±28.87	0.4735	0.1660	0.7565	0.1904
N_{200} (ms)	231.76±25.70	235.12±32.60	245.10±34.60	0.8628	0.1088	0.2403	0.1011
P_{300} (ms)	341.57±24.56	352.40±33.11	367.42±31.50	0.0417	0.0023	0.0218	0.0012
P300 Amplitude							
N_1-P_2 μv	8.07±5.75	7.70±5.32	5.60±3.85	0.9311	0.0495	0.0832	0.0336
P_2-N_2 μv	3.60±2.42	3.15±2.82	3.12±2.60	0.6849	0.6573	0.9981	0.6272
N_2-P_3 μv	12.03±4.92	11.40±5.60	10.92±2.50	0.7786	0.4709	0.8509	0.5037

Values expressed as mean ± SD; Analysis done by one way ANOVA. P-1: The *P* values between normotensives and prehypertensives. P-2: The *P* values between normotensives and hypertensives. P-3: The *P* values between prehypertensives and hypertensives. Group P: The *P* values of overall three groups. N100 (N1): Negative wave that appears in 100 ms from application of stimulus in ERP tracing; P200 (P2): Positive wave that appears in 200 ms from application of stimulus in ERP tracing; N200 (N2): Negative wave that appears in 200 ms from application of stimulus in ERP tracing; P300 (P3): Positive wave that appears in 300 ms from application of stimulus in ERP tracing.

The BHR were significantly increased in prehypertensives (P=0.0094) and hypertensives (P<0.001) compared to normotensives (**Table 1**). When the frequency domain and time domain parameters of short-term HRV were analyzed, the TP was reduced significantly (P< 0.001) among prehypertensives and hypertensives compared to normotensives. On expressing the absolute powers in normalized units, LFnu was elevated significantly (P<0.001) and HFnu was significantly decreased (P<0.001) in prehypertensives and hypertensives compared to normotensives. The LF-HF ratio was significantly elevated in prehypertensives (P= 0.0022) and hypertensives (P<0.001) compared to normotensives (**Table 1**). The analysis of the time domain parameters revealed that there was a highly significant decrease (P< 0.001) in RMSSD and SDNN among prehypertensives and hypertensives compared to normotensives. The pNN50 and NN50 were significantly reduced in prehypertensives and hypertensives compared to normotensives (**Table 1**).

The 30:15 ratio (P=0.0335) and E:I ratio (P=0.0059) were significantly reduced in hypertensives compared to normotensives, though they were not significantly different between prehypertensives and normotensives. There was a significant increase in (P<0.001) ΔDBP_{IHG} during isometric handgrip in prehypertensives and hypertensives compared to normotensives. The P300 latency was significantly prolonged in prehypertensives (P=0417) and hypertensives (P=0023) compared to normotensives (**Table 2**). Though the amplitude of P300 wave for N_1-P_2 was decreased in hypertensive subjects (P=0.0495) compared to normotensive subjects, the difference was not statistically significant for other form of amplitudes. Prehypertensives and hypertensives showed significantly elevated HOMA-IR, hsCRP and TBARS, and decrease in TAS in prehypertensive and hypertensive group compared to normotensive group (**Table 3**).

Table 4 depicts the correlation of P300 with various important parameters like BMI, RPP, FBG, plasma insulin, HOMA-IR, TBARS, TAS, hsCRP, TP, RMSSD, SDNN and LF-HF ratio of all the three groups. There was significant correlation of all these parameters with P300 in hypertensive group. In prehypertensive group, all parameters were significantly correlated with P300 except FBG, insulin, TBARS and hsCRP, and there was no significant correlation with any of the parameter in normotensive group.

Tables 5 and **6** depict multiple regression analysis to demonstrate the independent association of P300 (as dependent variable) with BMI, RPP, HOMA-IR, TBARS, TAS, hsCRP and TP (as independent variables) in prehypertensive and hypertensive group, respectively. There was significant independent contribution of RPP,

Table 3. Comparison of biochemical parameters between normotensive (n=42), prehypertensive (n=54) and hypertensive (n=51) groups

Parameter	Normotensives (A)	Prehypertensives (B)	Hypertensives (C)	P-1 A vs. B	P-2 A vs. C	P-3 B vs. C	Group P
FBG (mg/dl)	79.09±9.59	82.70±8.20	86.80±8.30	0.1092	0.0001	0.0432	0.0002
Insulin (μU/l)	7.48±2.98	10.87±3.50	21.46±4.60	<0.0001	<0.0001	<0.0001	<0.0001
HOMA IR	1.47±0.63	3.95±0.84	4.34±3.29	<0.0001	<0.0001	0.5890	<0.0001
hsCRP (mmol/l)	2.24±1.92	5.60±2.25	11.60±6.40	0.0004	<0.0001	<0.0001	<0.0001
TBARS (μM)	1.03±0.73	1.88±0.88	2.35±1.10	<0.0001	<0.0001	0.0276	<0.0001
TAS (μM)	419.23±130.68	330.12±105.09	252.80±84.60	0.0002	<0.0001	0.0009	<0.0001

Values expressed as mean ± SD; Analysis done by one way ANOVA. P-1: The *P* values between normotensives and prehypertensives. P-2: The *P* values between normotensives and hypertensives. P-3: The *P* values between prehypertensives and hypertensives. Group P: The *P* values of overall three groups. FBG: Fasting blood glucose; HOMA-IR: Homeostasis model assessment of insulin resistance; hs CRP: high-sensitivity C-reactive protein; TBARS: Thiobarbituric acid reactive substance; TAS: Total oxidant status.

Table 4. Correlation of P300 with various important parameters of control, prehypertensive and hypertensive groups

Parameters	Normotensive group (n=42)		Prehypertensive group (n=54)		Hypertensive group (n=51)	
	r	P	*r*	P	*r*	P
BMI	0.092	0.148	0.225	0.045	0.310	0.009
RPP	0.167	0.112	0.262	0.035	0.450	0.000
FBG	0.032	0.256	0.210	0.078	0.260	0.041
Insulin	0.076	0.190	0.198	0.104	0.285	0.031
HOMA-IR	0.040	0.282	0.256	0.040	0.382	0.005
TBARS	0.030	0.257	0.218	0.054	0.290	0.011
TAS	0.025	0.268	-0.250	0.039	-0.317	0.008
hsCRP	0.080	0.162	0.195	0.110	0.261	0.041
TP	0.045	0.280	-0.270	0.032	-0.425	0.000
RMSSD	0.169	0.108	-0.296	0.010	-0.431	0.000
SDNN	0.085	0.152	-0.220	0.046	-0.268	0.038
LF-HF ratio	0.160	0.117	0.230	0.043	0.377	0.006

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; FPG: Fasting blood glucose; HOMA-IR: Homeostasis model assessment of insulin resistance; TBARS: Thiobarbituric acid reactive substance; TAS: Total anti-oxidant status; TP: Total power; SDNN: Standard Deviation of Normal to Normal interval; RMSSD: Square root of the mean squared differences of successive normal to normal intervals; LF-HF ratio: ratio of low frequency to high frequency power of heart rate variability.

HOMA-IR, TAS, and TP to P300 in prehypertensive group (**Table 5**) and significant independent contribution of RPP, HOMA-IR, TBARS, TAS, and TP to P300 in hypertensive group (**Table 6**).

Discussion

In the present study, the significant prolongation of P300 latency in prehypertensives and treatment-naïve hypertensives compared to normotensives (**Table 1**) indicates the significant neurocognitive impairment in these two groups of 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, and impaired memory and reduced abstract reasoning [26-31]. However, in most of these studies cognitive impairment was assessed using different questionnaires and scores [5, 16, 26]. Further, the age of the subjects in most of these studies was above 40 years. As such cognitive decline occurs physiologically after the age 40 years. Therefore, age above 40 years is a biological confounder for assessment of cognitive func-

Table 5. Multiple regression analysis to assess the independent association of P300 (as dependable variable) with various parameters (as independent variables) in prehypertensive group (n=54), after adjusting for gender

Independent variables	Standardized regression coefficient Beta	95% Confidence interval		*P* values
		Lower limit	Upper limit	
BMI	0.170	0.005	0.265	0.110
RPP	0.272	0.107	0.270	0.025
HOMA-IR	0.240	0.002	1.242	0.042
TAS	-0.285	0.003	1.210	0.017
TP	-0.334	0.018	2.250	0.008

P values <0.05 considered significant. The *P* value <0.05 was considered significant. P300: Positive wave at 300 ms in event-related potential tracing; BMI: Body mass index; SBP: Systolic blood pressure; HOMA-IR: Homeostasis model assessment of insulin resistance; TAS: Total anti-oxidant status; TP: Total power of heart rate variability.

Table 6. Multiple regression analysis to assess the independent association of P300 (as dependable variable) with various parameters (as independent variables) in hypertensive group (n=51), after adjusting for gender

Independent variables	Standardized regression coefficient Beta	95% Confidence interval		*P* values
		Lower limit	Upper limit	
BMI	0.187	0.007	0.290	0.102
RPP	0.282	0.102	0.265	0.010
HOMA-IR	0.246	0.003	1.380	0.037
TBARS	0.268	0.004	1.602	0.031
TAS	-0.277	0.004	1.235	0.026
hsCRP	0.156	0.009	0.168	0.130
TP	-0.358	0.017	2.277	0.007

P values <0.05 considered significant. The *P* value <0.05 was considered significant. P300: Positive wave at 300 ms in event-related potential tracing; BMI: Body mass index; SBP: Systolic blood pressure; HOMA-IR: Homeostasis model assessment of insulin resistance; TBARS: Thiobarbituric acid reactive substance; TAS: Total anti-oxidant status; TP: Total power of heart rate variability.

tion in general population. Hence, in the present study we had recruited subjects below the age of 40 years and P300 assessment was used for quantitative estimation of cognitive deficit. As such, there are no reports from Indian subcontinent on the study of the factors contributing to the cognitive loss in prehypertension and hypertension.

Previous studies have reported that the primary pathophysiologic mechanism involved in elevated blood pressure in prehypertension and hypertension is the sympathovagal imbalance [17, 18]. In the present study, LF-HF ratio, the indicator of sympathovagal imbalance [32] was significantly elevated in both the groups (**Table 1**), indicating a considerable autonomic imbalance in prehypertensives and treatment naïve hypertensives. The LF-HF ratio was significantly correlated with P300 in both the groups, but not in control groups (**Table 4**), which suggests of a possible association of sympathovagal imbalance with cognitive impairment in prehypertensives and hypertensives. All the time-domain indices of HRV (RMSSD, SDNN, NN50, pNN50) were significantly reduced in prehypertensive and hypertensive groups compared to control group (**Table 1**). As time-domain indices are markers of cardiac vagal drive [23, 32], these findings reflect a substantial reduction in parasympathetic autonomic modulation in prehypertensives and hypertensives. The decreased cardiovagal modulation was further supported by reduced HFnu and TP of HRV (**Table 1**), as HFnu is the sign of vagal drive and TP is the marker of overall cardiac vagal modulation [32]. Thus, findings of the present study represent a significantly decreased cardiovagal modulation in both prehypertensive and hypertensive subjects. Significant decline in 30:15 ratio and E:I ratio in prehypertensives and hypertensives (**Table 1**) indicates the diminu-

tion in parasympathetic reactivity in these subjects, as these two parameters correspond to vagal reactivity [24]. Significant increase in ΔDBP_{IHG} in prehypertensives and hypertensives signifies increased sympathetic reactivity in these subjects, as ΔDBP_{IHG} represents sympathetic reactivity [24]. Thus, the autonomic imbalance in subjects with prehypertension and hypertension is expressed as augmented sympathetic activity and reactivity, and diminished vagal activity and reactivity. Further, decrease in TP of HRV, the major determinant of decreased cardiovagal modulation had independent contribution to P300 in prehypertensives (**Table 5**) and hypertensives (**Table 6**) as demonstrated by multiple regression analysis. These findings indicate that there might be a possible link of decreased cardiovagal modulation to the memory loss in prehypertensive and hypertensive subjects.

There are reports of metabolic derangements in prehypertension and hypertension [17]. There is also report of decline in cognitive function in conditions of metabolic derangements like dyslipidemia, insulin resistance (IR) and oxidative stress [33-35]. To best of our knowledge, till date there are no reports of cognitive impairment in prehypertensives, especially in Indian population. In the present study, HOMA-IR was significantly increased in prehypertensives and hypertensives compared to normotensives (**Table 3**). Persistent hyperglycemia, hyperinsulinemia and advanced glycation end-products (AGEs) play a primary role in the genesis of memory loss, brain aging and Alzheimer's disease [33, 34]. In Alzheimer's disease, IR has been reported to be one of the major factors for the development of cognitive impairment [35]. In the present study in prehypertensives and hypertensives, HOMA-IR had independent contribution to P300 as demonstrated by multiple regression analysis (**Tables 5** and **6**). Thus, it seems IR could be linked to the cognitive impairment in both prehypertensive subjects and hypertensive patients.

Another linking mechanism of cognitive deficit in hypertensives could be the oxidative stress, as level of TBARS was significantly increased and total antioxidant capacity (TAC) was significantly decreased in both prehypertensive and hypertensive groups compared to normotensive group (**Table 3**), Further, TAS was significantly correlated with P300 in both the groups (**Table 4**) and TAS had significant independent contribution to P300 in these subjects (**Tables 5** and **6**). Thus, oxidative stress may possibly have contributed to the cognitive deficit in prehypertensive and hypertensive patients. Though hsCRP, the common marker of inflammation was considerably higher in both prehypertensives and hypertensives, it was not correlated with P300 in these subjects. Therefore, retrograde inflammation is unlikely to be involved in the the memory loss in these subjects.

Memory impairment has been reported to be associated with obesity [36, 37]. Though BMI was significantly high in hypertensives, and there was positive correlation of BMI with P300 in these subjects (**Table 4**), the independent contribution of BMI to P300 was not significant (**Table 5**). Moreover, increase in BMI was not significant in prehypertensives compared to normotensives. Thus, it is less likely that increased BMI is linked to memory loss in prehypertensives and hypertensives.

Brain infarction is a common complication of hypertension [38]. Brain infarction and white matter diseases are reported to have a role in impairment of cognitive function [39, 40]. Therefore, cerebrovascular mechanisms have been proposed to be involved in the cognitive loss in hypertensives. Hyperinsulinemia, IR, oxidative stress and deposition of amyloid β proteins and AGEs in the brain substance have been proposed as non-cerebrovascular mechanisms in the cognitive deficit in diabetes [41, 42]. The limitations of the present study are that we have not performed amyloid β proteins estimation and brain imaging investigations for assessing pathophysiological basis of cognitive impairment. However from the findings of the present study, it appears that the decreased cardiovagal modulation might be a possible physiological basis of cognitive impairment in both prehypertensives and hypertensives, as it has been reported that chronic autonomic imbalance with heightened sympathetic tone leads to vascular wall hypertrophy with narrowing of vessel lumen resulting in reduced cerebral perfusion that might be an important part of the cerebrovascular component causing cognitive deficit [43]. Moreover, the influence of cardiovagal modulation on the physical expression of memory loss measured by MCE scale, MMSE or similar methods has not been

assessed in the present study. Therefore, a causal relationship between the cardiovagal modulation and cognitive impairment can't be established in the present study. Future studies should evaluate the association of the cerebrovascular profile and physical expression of memory loss with cardiovagal modulation in prehypertensive and hypertensive patients having cognitive impairment. The cognitive impairment in young prehypertensives, which was comparable to treatment naïve hypertensives in the present study, is an indicator of grave socioeconomic concern as prehypertension remains silently for many years before clinically manifesting as hypertension. As such decreased TP of HRV is an established CV risk [32]. Therefore, insulin resistance and oxidative stress along with decreased TP could make prehypertensives and hypertensives vulnerable to cardiometabolic risks, which could be linked to the neurocognitive impairment in these subjects.

The present study is the first report from Indian subcontinent comparing possible link of cardiovagal modulation with neurocognitive deficit in prehypertensive and treatment-naïve hypertensives in subjects below the age of 40 years. This is also the first report assessing the contribution of autonomic imbalance, oxidative stress and insulin resistance to neurocognitive deficit in hypertensive patients evaluated by estimation of P300, before the initiation of treatment. Thus, findings of the present study demonstrate that even before the clinical diagnosis of hypertension, these subjects have considerable impairment of memory in their prehypertension phase. In developing countries of south Asia, hypertension may not be detected early in the general population and treatment-compliance to hypertension may not remarkably be effective. Therefore, impairment of cognitive function in patients suffering from chronic conditions like prehypertension and hypertension, particularly in younger population could pose a grave risk to socioeconomic development in Indian subcontinent.

Disclosure of conflict of interest

None.

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