# EFFECT OF ANTIHYPERTENSIVE TREATMENT ON COGNITIVE FUNCTIONS ASSESSED BY EVENT RELATED POTENTIAL P300

**Physiology**

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## ABSTRACT

**Background:** Hypertension may result in cognitive decline. It is still not well established that treating the hypertension reduces the cognitive decline or not. Therefore the present study was planned to assess the effect of hypertension on cognitive functions by event related potential (ERP) P300 and effect of antihypertensive therapy on cognitive functions if any.

**Material and Methods:** The study compared the cognitive functions using ERP P300 among three groups comprised of 30 newly diagnosed hypertensives, 30 hypertensives undergoing treatment and matched controls.

**Result:** Newly diagnosed hypertensive had increased P300 latency and decreased P300 amplitude indicating their cognitive impairment. P300 latency was significantly less in patients on treatment than newly diagnosed hypertensives signifying that cognition improved with treatment. But still there was significant difference between patients taking treatment and controls in relation to P300 parameters which implied that even after treatment cognitive functions did not return up to normal level.

**Conclusion:** There is definite decline in cognition amongst untreated hypertensive subjects which could be detected with ERP P300 test. Antihypertensive treatment can reduce or slows down cognitive decline as well as improve the cognitive functions in hypertensive patients.

## KEYWORDS

Antihypertensive treatment, cognitive functions, Event Related Potential P300

## INTRODUCTION

Hypertension refers to the high blood pressure. It has been redefined recently in 2017 as systolic blood pressure (SBP) of $\geq 130$ mmHg and/or diastolic blood pressure (DBP) of $\geq 80$ mmHg based on an average of $\geq 2$ careful readings obtained on $\geq 2$ occasions.[1] earlier, hypertension refers to systolic blood pressure (SBP) of $\geq 140$ mmHg and/or diastolic blood pressure (DBP) of $\geq 90$ mmHg based on average of two or more readings taken at each of two or more visits.[2] Hypertension can affect almost all body organ-systems. The nervous system involvement in hypertension can even affect cognitive functions along with motor or sensory functions. Cognitive functions are the sequence of mental processes in response to some information. It includes getting the information, understanding it, storing it in an organized manner and later on recalling the information from stored memory when needed. Thus cognitive functions help a person to perceive, learn, remember and think about any information. Cognitive dysfunctions include defects e.g. disorientation in space & time, progressive loss of memory, and emotional depersonalization etc.[3-5]

Many studies found the association between hypertension and cognitive decline [3,6] but a few studies reported no association between hypertension and cognitive impairment.[7] It was also researched that decreasing or controlling blood pressure in hypertensives might reduce cognitive deterioration. Few studies observed reduction in cognitive impairment by using antihypertensive treatment[8-10] whereas others found no effect[11]. These types of studies used subjective tests like Mini Mental State Examination (MMSE), Digit Symbol Test or electrophysiological Endogenous/Event Related Potential (ERP) P300 test. ERP P300 was able to find early subclinical cognitive dysfunctions which were not detected by other subjective tests.[12] So ERP P300 was used to assess cognitive functions in present study.

ERP records the electrical responses of brain to external stimulus. There are many wave-forms e.g. P65, Nd, N2, P3 (P300), P4, and N400. The latency of P300 wave is inversely related with mental function; higher the latency more will be the cognitive decline. Therefore it is used as an objective electrophysiological index for assessing cognitive function. P300 amplitude represents the neural activity related to memory when one type of stimulus comes after the other type of stimulus i.e. when stimulus context is updated. It acts as an index to measure the attention allocated by individual to a given task. Higher the P300 amplitude superior the memory performance and attention allocated to a task.[13,14] De-quesada et al found delayed P300 latency and decrease in its amplitude in uncomplicated

hypertensive patients.[15] Whereas Cicconetti et al did not find significant differences for P300 latency between hypertensives and normotensives.[16] Few studies affirmed that antihypertensive treatment significantly decreases the rate of cognitive decline in hypertensive patients.[9,11] But one another study found that cognitive decline in hypertensive patients was not significantly different from subjects on placebo.[17]

Keeping in view all the inconclusive information about the association of hypertension and its treatment with cognitive decline, the present study was planned to assess the effect of hypertension on cognitive functions by event related potential P300 and role of antihypertensive therapy on cognitive functions if any.

## AIMS AND OBJECTIVES
1. To study the effect of hypertension on the cognitive functions.
2. To study the effect of antihypertensive drug treatment on the cognitive functions.

## MATERIAL AND METHODS

The present study was conducted in department of Physiology; PGIMS, Pt. B. D. Sharma UHS, Rohtak in collaboration with the department of Medicine. Ethical clearance was obtained from the related institutional committee (Pre-Clinical P.G. Board of Studies). The study included 90 subjects, which were divided into three groups:

Group I: comprised of 30 healthy, age and sex matched control subjects.

Group II: comprised of 30 newly diagnosed patients of essential hypertension of either sex, in age group of more than 40 years.

Group III: comprised of 30 patients of essential hypertension of either sex, in age group of more than 40 years undergoing drug treatment for more than 5 years.

Informed written consent was taken from each subject. Then a detailed history was taken, clinical examination was done and investigations were recorded. Cognitive functions were assessed by ERP P300 test.

### Inclusion Criteria[2,3,16]
Patients newly diagnosed with essential hypertension as they had SBP $\geq 140$ mmHg and/or DBP $\geq 90$ mmHg based on an average of $\geq$ two readings taken at each of two or more visits (study was carried out and

completed before 2017) and patients who were using antihypertensive drugs for more than 5 years.

### Exclusion Criteria[3,16]

Subjects with more than 25 decibel loss, altered sensorium, neurological or psychiatric illness, endocrinopathies, secondary hypertension, history of drug abuse, and those who did not cooperate during the study period were excluded on the basis of history, clinical examination and investigations e.g. blood pressure, complete heamogram, routine urine examination, lipid profile, glycemic levels, liver function test, and renal function test etc.

### Procedure for Event related potential P300[16,18-21]

Subjects were well informed about the procedure of P300 recording. ERP P300 procedure was carried out as per standardized instructions given in table 1. The signals were picked by electrodes and then filtered, amplified, averaged and recorded by machine. With rare stimulus, a negative N1- positive P2 – negative N2 – positive P3 complex was observed. Average of two reproducible recordings was taken as the final value of P300 latency and amplitude.

### Table 1: ERP P300 procedure

| Machine / Equipment used | RMS EMG EP MK II equipment (Recordings and Medicare Systems Private Limited, Electromyography & Evoked Potential machine, model - Mark II, Chandigarh, India) |
|---|---|
| Method Used | Auditory Oddball Paradigm in soundproof room |
| Precautions | Subject should be at ease, relaxed, comfortably lying on a bed, instructed to keep eyes closed but avoid sleep |
| Stimulus parameter | Auditory tone, 70 dB above hearing threshold, binaural, via head-phone, rate 1.1/s, total number – 300 |
| Rare Tone | 2000 Hz, 20% of total tones, occurring randomly |
| Frequent Tone | 1000Hz, 80% of total tones |
| Ag/AgCl electrodes placed as per 10–20 International system of placement | One active electrode on vertex labeled as Cz and one as ground electrode to forehead termed as Fpz. Two reference electrodes were attached to right and left mastoid (A1 and A2). All the electrodes were plugged to a junction box. |
| Skin to electrode impedance | below 5 K ohms |
| Band pass filter | 0.2 -100 Hz |
| Instruction to subject | Mentally count the target tones and then report the total number of target tones counted at the end of test procedure. |

### STATISTICS

All the data so obtained were subjected to appropriate statistical analysis by using ANOVA with post hoc Tukey's test using SPSS 15 software and p value < 0.05 was taken as significant.

### RESULTS

The differences in age, sex, weight, height, and body mass index were not significant among groups (table 2). Also there were no significant differences among groups in relation to hemoglobin, glycemic levels and lipid profile. Hence all the three groups were anthropometric and biochemical profiles wise matched.

A significant difference between the systolic and diastolic blood pressure among the groups I & II and II & III were noted. Systolic blood pressure of group I was not significantly different from group III, but the diastolic blood pressure of group I was significantly lower than that of group III. All the three groups were significantly different from each other in view of P300 latency. In case of P300 amplitude, there were significant differences between groups I & II and groups I and III but not between II & III (table 3).

### Table 2: Anthropometric profile of groups

| Parameters | Group I (n=30) Mean± S.D. | Group II (n=30) Mean± S.D. | Group III (n=30) Mean ± S.D. | p- value |
|---|---|---|---|---|
| Age (years) | 55.96±7.38 | 55.86±8.33 | 59.6±8.03 | NS |
| Sex (M /F) | 20/10 | 20/10 | 20/10 | NS |
| Ht (cm) | 162.46±5.56 | 163.76±8.34 | 161.93±10.42 | NS |
| Wt (kg) | 62.5±7.24 | 63.66±5.07 | 66.33±7.97 | NS |
| BMI (%) | 23.69±2.68 | 23.89±2.87 | 25.51±4.03 | NS |

NS- non-significant among groups (p > 0.05)

### Table 3: Blood pressure and cognitive functions of groups

| Parameters | Group I (n=30) Mean ± S.D. | Group II (n=30) Mean ± S.D. | Group III (n=30) Mean ± S.D. |
|---|---|---|---|
| SBP (mm Hg) | 122.4 ± 4.79* | 160.73 ± 8.12** | 125.8 ± 6.06 |
| DBP (mm Hg) | 80.0± 3.4* | 106.06 ± 5.78** | 84.06 ± 5.47*** |
| P300 latency (ms) | 283.7 ± 9.69* | 302.98 ± 13.1** | 293.35 ± 11.42*** |
| P300 amplitude (µv) | 6.88 ± 2.14* | 3.64 ± 1.7 | 3.96 ± 1.38*** |
| p- value significantly different between groups * I and II, ** II and III and *** I and III | | | |

### DISCUSSION

In present study, newly diagnosed hypertensives had significantly higher blood pressure than controls. Subjects on anti-hypertensive treatment exhibited that their systolic blood pressure was near to control group and diastolic blood pressure was still significantly higher than control but was in normotensive range. The present study affirmed that the newly diagnosed hypertensive patients had cognitive impairment and were revealed by increased P300 latency and decreased P300 amplitude when compared to controls. Various studies supported this observation. Tandon et al reported similar results in middle aged hypertensives.[22] P300 was found to be affected in hypertensive patients who did not have any cognitive dysfunction symptoms. There the delayed P300 latency represented subclinical cognitive impairment.[9] It was suggested that cognitive impairment associated with change of ERP can be due to decreased cortical blood flow and hemodynamic changes in the central nervous system.[15,23] Hypertensive subjects have more instances of cerebral atrophy, white matter lesions and reduced brain volume.[24] All this can also affect P300 generators e.g. hippocampus, temporo-parietal region and various association areas of neocortex which can cause delay in sensory information processing and memory updating leading to abnormal P300 latency and amplitude.[22,25] Guo Z et al hypothesized that a minimum particular level of systolic pressure of at least 130 mmHg is must to keep cerebral perfusion normal and hence help to maintain normal cognition.[8] Contrary to our study Cicconetti et al found that there was no significant difference for P300 latency between hypertensives and normotensives.[16]

In our study, hypertensive patients were treated by using the combined drug treatment e.g. diuretics with other agents such as ACE inhibitors, beta blockers, or calcium channel blockers. The P300 latency was significantly less in group III than group II indicating that cognition improved with treatment. P300 amplitude did not reveal any significant difference between groups III and II indicating that it is not very sensitive to identify cognitive difference which can be easily recognized by P300 latency (table 3). In totality, significantly better P300 latency indicates significant improvement in cognition in patients on antihypertensive treatment than newly diagnosed hypertensives. But still P300 latency and amplitude were significantly different in patients on treatment than controls. It means that even after the treatment, cognition parameters improve but did not return up to normal levels (table 3).

Many studies reported similar results. Clonidine treatment produced the decrease in P300 amplitude but the P300 latency was unaffected.[26] When hypertension was treated in hemodialysis patients, P300 parameters got improved suggesting that hypervolemia may be one of the modifiable factors of cognitive dysfunction in these patients.[27] Ramipril therapy also improved the P300 latency and hence cognitive functions by affecting serum nitrite and lipid peroxidation pathway.[28] In contrary to our study, there were few reports suggesting that certain types of antihypertensive drugs are not protective against cognitive decline in hypertension subjects which could be explained on the basis

of the difference in designs of different studies, their sample sizes, the different tests and methods used to assess cognitive function and definition of dementia.[29,30]

The present study revealed that antihypertensive treatment can improve cognitive functions of patients. But cognitive functions can't be brought back to normal. Thus as per this study, treating blood pressure is important as it significantly reduces cognitive decline in hypertensive patients.

## CONCLUSION

There is definite cognitive decline in untreated hypertensive subjects which can be detected with ERP P300 test. Antihypertensive treatment can reduce cognitive decline or improve the cognitive dysfunction in hypertensive patients. So it is suggested that ERP P300 should be inducted in routine investigation for hypertension patients for early diagnosis of cognitive decline and to assess improvement in cognition following treatment of hypertension.

## LIMITATIONS

1. In the present study, the number of females in control and test groups was less. A larger number of female subjects could help in getting better and more reliable results as well as comparison between male and females.
2. Effect of different combinations of antihypertensive drugs should have been studied separately. So there is a scope for further research.
3. The study was performed before the declaration of new guidelines regarding diagnosis of hypertension.

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