Original Article

Effect of Pulse Pressure on Cognitive Function

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Abstract

Background: Although the effects of blood pressure on cardiovascular events and cognition have been reported widely in literature, the effect of pulse pressure on cognition has received less attention.

Methods: In this study, 65 male subjects with essential hypertension, not on any treatment, with a pulse pressure of more than 60 mmHg (mean pulse pressure-70.76±11.5 mmHg) were evaluated. Mini Mental State Examination and Event related potentials (P300 and N200) were used for assessment of cognitive function. 65 age and sex matched non-hypertensive controls with a pulse pressure less than 60 mmHg (mean pulse pressure-43.87±8.79) were taken as controls.

Results: Compared to controls (P300 latency- Fz-310.2 ± 16.71, Cz- 305.3 ± 16.10, Pz- 316.1 ± 14.55. N200 latency- Fz- 193.4 ± 11.78, Cz- 187.3 ± 12.36, Pz- 198.3 ± 15.21), the cases had increased latency of P300 and N200 waveforms (P300 latency- Fz -367.72 ± 14.35, Cz- 361.36 ± 16.77, Pz- 375.45 ± 14.98. N200 latency- Fz- 243.21 ± 9.33, Cz- 231.0 ± 12.57, Pz- 248.22 ± 10.51) signifying impaired cognitive functions.

Conclusion: Increased pulse pressure, in patients of essential hypertension between 30-50 years, without overt dementia, is associated with subclinical cognitive impairment as evidenced by prolonged latencies on ERPs.

Key words: Pulse pressure; cognition; P300; event related potentials; hypertension

Introduction

The current guidelines for the management of hypertension rest almost completely on the measurement of systolic and diastolic blood pressures, two specific inflection points of the blood pressure (BP) wave, which are usually considered in isolation [1,2]. However, BP propagates through the arterial tree as a repetitive continuous wave and is more accurately described as consisting of a pulsatile component (pulse pressure) and a steady component (mean pressure) [3]. Pulse pressure is the difference between systolic and diastolic BP and depends on ventricular ejection, arterial stiffness and the timing of wave reflections.

A few population based studies have linked high blood pressure to an increased risk of cardiac and cerebrovascular events [4,5,6]. Vascular risk factors have also been linked to the pathogenesis of cognitive disorders and dementia [7]. However, the potential damage on cognitive function by the different BP components is less clear and has not been examined to the same extent as BP effects on cardiovascular disease and total mortality. Since increased pulse pressure is a clinical indicator of arterial stiffness, it could be postulated that functional changes of the arterial system are involved in the pathogenesis of cognitive decline and dementia [8]. Nonetheless, research so far has failed to establish a link between raised pulse pressure and cognitive decline.

Mini Mental State Examination (MMSE) is a brief, objective assessment of cognitive functioning and is a reliable and validated measure of changes in cognitive status [9]. Analysis of event-related potentials (ERP) has been recommended for detecting early cognitive dysfunction, not usually detected by traditional methods of assessment of cognitive function [10]. Numerous clinical P300 studies [11-13], strongly suggest that this ERP

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component, elicited by auditory, visual, olfactory or somatosensory stimuli [14], may be clinically useful as an index of cognitive function. P300 wave may represent short duration memory functions and pre-attentive storage taking place in sensory cortex [15]. N200 wave may indicate an early cognitive elaboration concerning subject's attention orientation [16]. Particularly the latency of P300 and N200 components, have been found to increase with increasing cognitive deficit [10]. In the present study, these components of ERPs have been assessed along with MMSE for cognitive assessment in early and untreated cases of essential hypertension with increased pulse pressure, without overt dementia, to explore whether raised pulse pressure can be an independent risk factor for cognitive decline. It was anticipated that if such an association is found, it may prove to be a predictive marker, which will help plan timely intervention to preserve cognitive function with an individual's increasing age.

Methods

A cross sectional, case control study was conducted wherein subjects were selected by screening patients from the outpatient departments of Lok Nayak Hospital by measurement of right arm blood pressure by a mercury sphygmomanometer. Sixty-five hypertensive males, aged 30-50 years with pulse pressure more than 60 mmHg were recruited into the study [17]. Prior to participation, all participants gave their written, informed consent for the study, which had received approval of the Institutional Ethics Committee. The importance of demographic variables has been stressed when examining association between BP and cognitive performance [18] and therefore, demographic data such as age (in years), education (in years) and occupation (level) was carefully recorded for each subject. Occupation was coded on a scale from 1 (unskilled) to 6 (executive/professional). Body mass index (BMI) was calculated for all subjects.

Subjects were restricted to age group 30-50 years as age related changes in event related potentials have been documented [19]. Females were excluded as ERPs are known to vary with the menstrual cycle [20]. Only those subjects not on any antihypertensive medication were included. Those with any obvious vascular or psychiatric disease, secondary hypertension or diabetes were excluded by careful recording of history, physical examination and by doing random blood sugar levels, serum electrolytes, serum creatinine, serum urea, lipid profile, urine examination (for protein, glucose, blood and microscopic examination), chest X-ray, ECG and renal ultrasound. Overweight and obesity were classified according to 1998 National Institute of Health Guidelines [21].

Blood Pressure Measurement

Blood pressure was measured twice on the same patient, once on the screening day, and again on the test day. It was measured on the right arm in sitting position, as per the recommendations of the Canadian Hypertension Education Program [22]. Mean of the two readings was taken. Pulse pressure was defined as the difference between the systolic and the diastolic blood pressure. Only those subjects with pulse pressure more than 60 mmHg were included.

Sixty-five age and sex matched non-hypertensive controls, with pulse pressure less than 60 mmHg who were apparently healthy by history and thorough physical examination were also included in the study. MMSE and ERPs were assessed for this group also.

MMSE is a validated and reliable test for cognitive mental state and is useful in quantitatively estimating the severity of cognitive impairment and in serially documenting cognitive change [23]. The global cognitive assessment was based on the MMSE performed by the physician. A value less than 24 was considered to indicate cognitive impairment [23].

Event Related Potentials Recording

ERPs are generated by patient's response to auditory, visual or other sensory stimuli. Auditory stimuli have been used in this study. An auditory cognitive ERP is generated by playing a baseline series of frequently occurring rhythmic auditory stimuli for a subject and then presenting secondary auditory stimuli (rare stimulus) at random. The subject mentally counts the secondary auditory "oddball" (rare) stimuli, and this specific intellectual function generates a discrete waveform of cognitive evoked response called the P300 component because its latency is about 300 ms (millisecond) after the stimulus [24].

EBNeuro machine (Evoked potential measuring system- Galileo NT) supplied by Firenze, Italy was used to record the Evoked Potentials. The evoked potentials were recorded as per the guidelines of

International Federation of Clinical Neurophysiologists (IFCN) [25]. The examination was conducted in uniform conditions in all the subjects. The subjects assumed a comfortable position in a standard audiometric, sound proof, and air conditioned room so that they were relaxed. During the P300 recording session subject was instructed to fixate his eyes on a particular spot on the ceiling in order to avoid artifacts due to eye movements and improve his concentration and attention to target stimulus. Silver/silver chloride disc electrodes were used. First the scalp sites were cleaned with a cotton pad moistened with alcohol. The site was wiped with dry gauze to remove the oil from the skin. The site was rubbed with an appropriate amount of Neuprep skin prepping jelly to abrade the skin for impedance reduction and the site was further cleaned with a dry piece of gauze. The disc electrodes with 10-20 EEG conducting paste were applied to the sites and covered with a swab of cotton and the edges of the cotton pressed. The active electrodes were placed using the 10-20 international system on Fz, Pz and Cz sites referred to linked earlobes with a forehead ground. Electrode to skin impedance was kept below 5 kilo-ohms. The method was fully explained to all the subjects to get the best compliance.

P300 was measured in response to random application of two types of stimuli. "Odd-ball" acoustic paradigm was adopted, 200 stimuli were presented of which 40 were the rare or the target stimuli. 80 percent of the tones were frequent (500 Hz stimuli) and 20 percent were rare (2000 Hz stimuli), randomly received by patients. Acoustic stimuli were of 80 dB each. Linear tone with a starting condensation phase with a plateau phase of 100ms, rise/fall of 10ms and a rate of once every one second was used. The signals were in phase at the two ears. The Galileo NT settings were selected so as to filter the evoked responses to the frequent and the rare stimuli with a band pass of 0.1-20 Hz and averaged simultaneously for 40 responses.

The P300 wave was identified as the largest positive peak occurring for all electrode sites after the N100-P200-N200 complex with latency more than 250ms. The latency and amplitude of the waveform were recorded. The latency was calculated from the point of stimulation.

The quality of cognitive response is related to amplitude and latency of the P300 wave, with higher amplitudes and shorter latencies being associated with improved cognitive function [26].

Statistical analysis

Data was analyzed using SPSS 17.0 software (SPSS, Chicago, Illinois, USA). Groupwise descriptive statistics of parameters are displayed as mean ± SD. The two groups were compared using unpaired student t test. P value <0.05 was considered significant. Pearson's linear correlation coefficient was calculated by preparing a correlation matrix. Only those correlations with $p<0.05$ were considered significant.

Results

The characteristics of study and control subjects are summarized in Table 1. There was a significant difference between systolic BP of cases and controls

Table 1- Characteristics of the study and control population

	Controls (n=65)	Cases (n=65)	p value
Age (years)	39.32 ± 7.59	43.22 ± 6.32	NS
Systolic BP (mm Hg)	123.30 ± 12.48	159.84 ± 14.82	<0.001
Diastolic BP (mm Hg)	81.36 ± 9.12	84.07 ± 10.95	<0.05
Pulse pressure (mm Hg)	43.87 ± 8.79	70.76 ± 11.50	<0.001
BMI (kg/m^2)	24.99 ± 3.99	28.47 ± 4.53	NS
Heart Rate (/min)	67.45 ± 11	70.75 ± 11.41	NS
Education (years)	10.5 ± 3.9	8.6 ± 4.6	NS
Occupation (Level 1-6)	3.5 ± 1.8	4.2 ± 2.8	NS

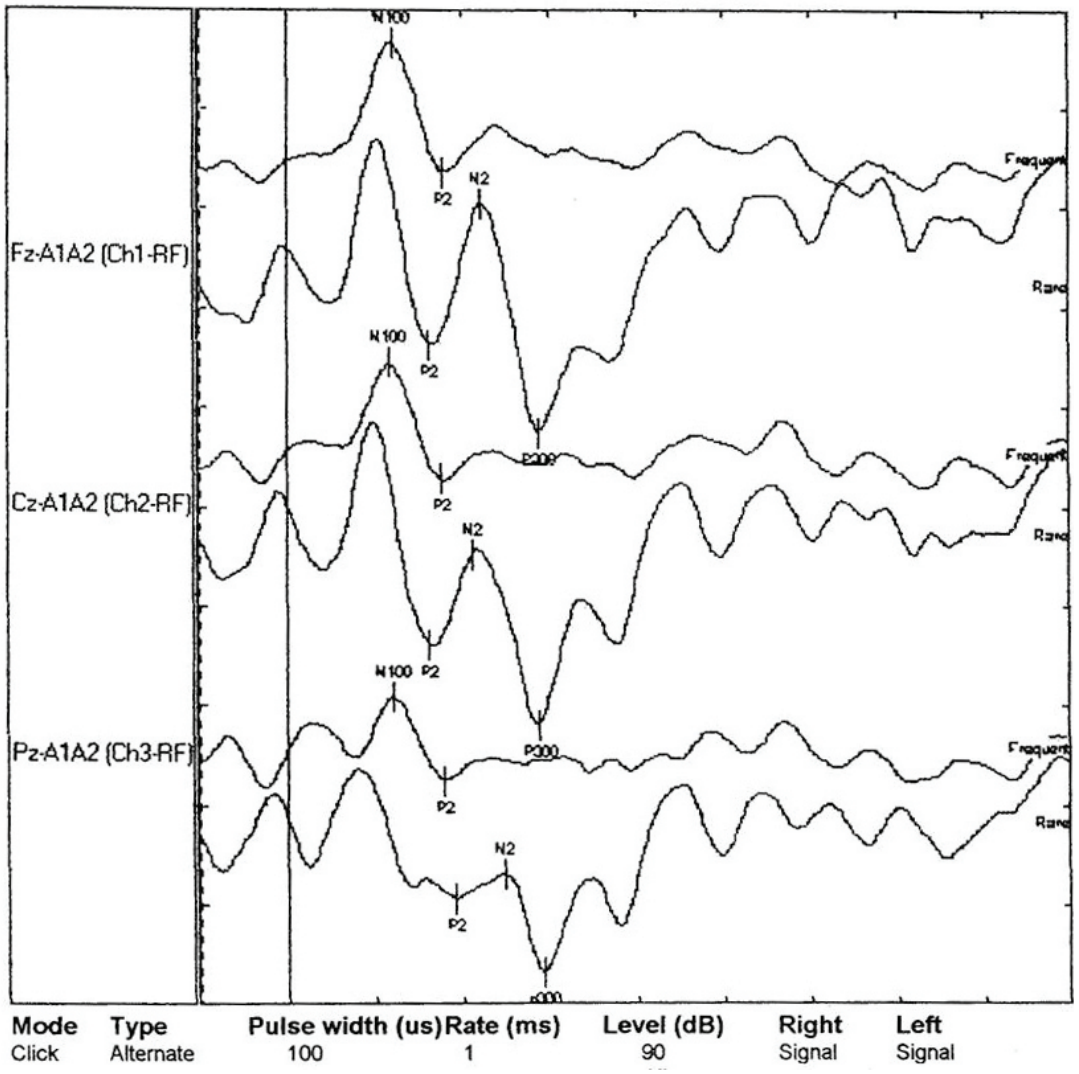

Figure 1- P300 and N200 waveforms recorded at three electrode sites, Fz, Cz and Pz.

Table 2- Evoked potentials and MMSE in the two groups

		Controls (n=65)	Cases (n=65)	p value
N200 latency (ms)	Fz	193.4 ± 11.78	243.21 ± 9.33	<0.01
	Cz	187.3 ± 12.36	231.0 ± 12.57	<0.01
	Pz	198.3 ± 15.21	248.22 ± 10.51	<0.001
P300 latency (ms)	Fz	310.2 ± 16.71	367.72 ± 14.35	<0.01
	Cz	305.3 ± 16.10	361.36 ± 16.77	<0.01
	Pz	316.1 ± 14.55	375.45 ± 14.98	<0.001
P300 amplitude (ms)	Fz	5.75 ± 1.32	6.71 ± 2.56	NS
	Cz	6.12 ± 1.45	5.30 ± 2.11	<0.01
	Pz	6.45 ± 1.88	5.67 ± 2.61	<0.01
MMSE score/30		29 ± 1	27 ± 3	NS

($p<0.001$), and in diastolic BP values ($p<0.05$). Pulse pressure was also significantly ($p<0.001$) different between cases and controls. BMI, heart rate, education and occupation were similar in the two groups. Figure 1 shows the P300 and N200 waveforms generated during the study. The findings of the cognitive evaluation are summarized for both groups in Table 2. A significant positive correlation was derived by calculating Pearson's linear correlation between N200 latency at Pz and pulse pressure in cases ($r = 0.571$, $p<0.001$). There was also a positive correlation between P300 latency at Pz and pulse pressure ($r = 0.803$, $p<0.001$). There was no correlation between the P300 amplitude and pulse pressure. MMSE was similar in the two groups.

Discussion

The primary goal in this study was to assess effect of increased pulse pressure on cognition using MMSE and evoked potentials, in patients of untreated essential hypertension without dementia. The cases and controls had comparable age, BMI, heart rate, education and occupational levels and were all males. Out of the 65 hypertensive cases, 16 had isolated systolic hypertension. The MMSE score was similar in the two groups and can be attributed to the fact that it has a limited ability to pick up sub-clinical cognitive impairment [9]. None of the cases had a score less than 24 as dementia was one of our exclusion criteria. Evoked potentials in cases showed an increase in N200 and P300 latency at all three electrode sites, Fz, Cz and Pz. Amplitude of P300 was also increased at Cz and Pz. There was a significant correlation between N200 latency and P300 latency at Pz and pulse pressure. Therefore, this study indicates a significant association between raised pulse pressure and cognitive impairment as indicated by prolonged latencies. In the absence of obvious clinical cognitive impairment as indicated by comparable MMSE scores, the presence of prolonged latencies on ERP testing indicates presence of subclinical cognitive impairment in untreated hypertensive population with wide pulse pressure.

Several mechanisms may explain the present finding of an association between raised pulse pressure and cognitive impairment. Pulse pressure and arterial stiffness have been related to atherosclerosis in large [27] and small vessels [28]. Vascular mechanisms of cognitive impairment involve small vessel diseases, which are associated with small infarcts (lacunae), white matter lesions, and cortical brain atrophy. Cognitive impairment may be the direct consequence of ischaemic brain lesions, depending on the volume, location, and number of these vascular lesions [29]. In addition, abnormalities of the white matter may be associated with cognitive impairment [30]. An increased pulse pressure has been associated with the prevalence and severity of cerebral white matter lesions and in a recent study, aortic stiffness appeared as an independent predictor of stroke in patients with essential hypertension [30]. Indeed the presence of arteriosclerosis or lipohyalinosis of small vessels might be the origin of vascular cerebral lesions or chronic hypoperfusion of the white matter and thus contribute to the development of cognitive impairment.

Age related confounding factors affecting blood pressure and cognition [31] have been excluded in the present study by restricting the age group from 30-50 years. To screen a population for hypertension and to find untreated cases is difficult, which has resulted in a restricted number of cases in this study. This study has a few limitations. Information on vascular diseases was taken from the medical records of the patients. This might have led to the inclusion of some undiagnosed mild cases of vascular diseases. In addition, this is a cross sectional study, so does not have follow-up data on blood pressure and medication patterns or data on newly identified risk factors which may modify the effect of pulse pressure on cognition. Hence, despite the best of efforts to exclude several major confounders, some unknown confounding effects might still have been present.

The study indicates that increased pulse pressure, in patients of essential hypertension between 30-50 years, without overt dementia, is associated with prolonged latencies on ERPs , which represents sub-clinical cognitive impairment. The results are similar to those of Papaliagkas et al [32] that P300 and N200 latencies can be used as measures of mild cognitive impairment independent of the MMSE score. These results emphasise the necessity of longitudinal studies to determine whether therapeutic options aimed at reducing pulse pressure can maintain optimal cognitive function or attenuate its decline with increasing age.

Key Points

- The ill-effects of blood pressure on cardiovascular events and cognition is widely known
- The present study has studied the effect of pulse pressure on cognition in untreated hypertensives
- Wide pulse pressure is associated with sub-clinical cognitive dysfunction as evidenced in the form of prolonged latencies on event-related potentials

Conflict of interest: None declared.

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