The association between cognitive decline and short-term blood pressure variability in middle-aged patients with primary hypertension — a pilot study

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Streszczenie

Wstęp. Nadciśnienie tętnicze (HTN) jest częstą przyczyną rozwoju zaburzeń czynności poznawczych. Aktualne dane podkreślają rolę HTN w niekorzystnej przebudowie naczyń i promowaniu zmian w obrębie mikrokrążenia mózgowego, prowadzących do upośledzenia funkcji poznawczych. W prezentowanym badaniu szukaliśmy związku między dobową zmiennością ciśnienia tętniczego (BPV) z wykorzystaniem 24-h ambulatoryjnego monitorowania ciśnienia tętniczego (ABPM) a zaburzeniami funkcji poznawczych u pacjentów w średnim wieku obciążonych nadciśnieniem tętniczym.

Materiał i metody. Grupę badaną stanowiło 42 pacjentów z niepowikłanym nadciśnieniem tętniczym (24 kobiety, 18 mężczyzn, średni wiek: 59,1 ± 6,1 r.). BPV oceniono za pomocą ABPM i wyrażono w odchyleniu standardowym (24 MAP SD) i znormalizowanym względnym współczynniku zmienności (CV). Sprawność funkcji poznawczych oceniono z wykorzystaniem Krótkiej Skali Oceny Stanu Psychicznego (MMSE, *Mini-Mental State Examination*), Testu Rysowania Zegara (CDT, *Clock Drawing Test*), Montrealskiej Skali Oceny Funkcji Poznawczych (MoCA, *Montreal Assessment Cognitive Scale*).

Wyniki. W całej grupie badanej wyniki MMSE i CDT mieściły się w zakresie prawidłowym, jedynie w teście MoCA średnie wartości pozostawały poniżej przyjętej normy. Wyniki testów neuropsychologicznych były porównywalne dla grup z prawidłowym i nieprawidłowym (bez spadku nocnego) dobowym profilem BP. Spośród analizowanych parametrów BPV CV ujemnie korelował z wynikami CDT oraz MoCA. Podobnie, 24 MAP wyrażone odchyleniem standardowym korelowało ujemnie z wynikami CDT. W analizie wieloczynnikowej z uwzględnieniem wieku, płci, poziomu wykształcenia oraz zaburzeń lipidowych wyniki testu MoCA były odwrotnie skorelowane z CV. Średnie wyniki w teście MoCA były istotnie niższe u mężczyzn w porównaniu do kobiet.

Wnioski. W badaniu pilotażowym, łagodne upośledzenie funkcji poznawczych u chorych z wieloletnim, niepowikłanym nadciśnieniem tętniczym może być związane ze zwiększoną dobową zmiennością ciśnienia tętniczego.

Słowa kluczowe: upośledzenie funkcji poznawczych, zmienność ciśnienia tętniczego, nadciśnienie tętnicze

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Abstract

Introduction. Hypertension (HTN) is a common cause of cognitive dysfunction. Current data emphasize a role of HTN in the development of unfavourable vascular remodelling and changes in cerebral microcirculation, leading to cognitive decline. In this study, we sought associations between circadian blood pressure variability (BPV) in a 24h blood pressure ambulatory monitoring (ABPM) and cognitive decline in middle-aged hypertensive patients.
Material and methods. The study group comprised 42 patients with uncomplicated hypertension (24 females, 18 males; mean age: 59.1 ± 6.1 years). BPV was assessed by ABPM and expressed in standard deviation (24 MAP SD) and coefficient of variation (CV). Cognitive performance was evaluated using Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT) and Montreal Assessment Cognitive Scale (MoCA).
Results. In the whole study group, MMSE and CDT scores were within the normal range, but the mean scores were lowered in the MoCA test. All of the neuropsychological test scores were comparable in groups with normal and abnormal (non-dipper) blood pressure patterns. Among the analyzed BPV indicators, CV was negatively correlated with CDT and MoCA scores. 24 MAP expressed in standard deviations was also negatively correlated with CDT scores. In the multivariate analysis, MoCA scores were inversely associated with CV after adjusting for age, gender, education and abnormal lipid profiles. Mean MoCA scores were significantly lower in men in comparison to women.
Conclusions. In this pilot-based study, mild cognitive impairment in middle-aged patients with long-lasting uncomplicated hypertension may be associated with increased diurnal variability of blood pressure.

Key words: cognitive decline, blood pressure variability, hypertension

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Introduction

As a consequence of demographic changes related to population ageing, cerebrovascular mortality becomes a significant and increasing healthcare problem. Currently, cerebrovascular disease is the third most frequent cause of death in Poland. In addition, it is also one of the most frequent causes of cognitive dysfunction and vascular dementia (VD) [1–4].

Although the pathogenesis of small vessel disease has not been fully understood, an increasing body of evidence suggests a role of elevated blood pressure in the development of small vessel disease in the network of cerebral arteries [5, 6]. Arterial hypertension (HTN) influence vascular remodelling and progress of atherosclerosis with ageing leading to hypoperfusion of the central nervous system and, as consequence, to the development of ischemic lesions, lacunar strokes and damage of the white matter [7]. Additionally, recent studies have emphasized the potential role of the cerebral renin-angiotensin-aldosterone system (RAAS) in the development of VD and cognitive disorders. RAAS has been found to have an impact on the control of cerebral blood flow, local oxidative processes, and the course of local inflammatory response [1, 8].

Currently, a close relationship has been well established between HTN and dementia in the elderly. However, some cross-sectional studies suggest an adverse effect of hypertension on cognitive functions also in the younger age groups [9–11]. Earlier reports demonstrated that accumulated blood pressure load proportionally increase the risk of cerebrovascular complications including VD [12–20], and the enhanced analysis of conventional 24-hour ambulatory blood pressure monitoring (ABPM) data may be useful in predicting cardio- and cerebrovascular outcomes [21–25]. It has been showed that the assessment of short-term systolic blood pressure variability (BPV) and pulse pressure (PP) substantially increase the prognostic value of data derived from conventional ABPM [26]. There have been only a few data in the available literature on the relationship between BPV and cognitive impairment but they yielded inconclusive results [27–29].

In this pilot study, we aimed to assess the association between BPV and cognitive function in middle-aged patients with uncomplicated primary HTN.

Material and methods

Study population

The study group comprised 42 patients (24 females, 18 males) aged 45–70 years with spontaneous and uncomplicated hypertension who were referred to the Department of Hypertension & Internal Diseases in Szczecin from November 2017 to March

2018 (inclusive). In reference to medical standards, secondary hypertension was excluded based on the routine biochemical and hormonal test and radiological imaging. The study protocol was approved by the Bioethical Committee at the Pomeranian Medical University in Szczecin (KB-0012/53/18). All subjects participating in the study gave their written informed consent.

24-h ABPM protocol

In all cases, a 24-hour ABPM was performed using Spacelabs 90207 device. Automatic measurements were taken every 20 minutes during the day and every 30 min during the night. Hours from 6.00 to 22.00 were set as a daytime and from 22.00 to 6.00 as a nocturnal period. We analyzed 24-hour, daytime and nocturnal systolic, diastolic and mean blood pressure (24SBP, 24DBP, 24MAP, SBPd, DBPd, MAPd; SBPn, DBPn and MAPn, respectively), and nocturnal fall in systolic blood pressure. According to current guidelines [30], dipping blood pressure profile was defined as a reduction of at least 10% in overnight blood pressure; non-dipping as a decline less than 10%: extreme-dipping as a decline above 20%, and reverse dipping if blood pressure was higher at night. As an additional indicator of the short-term circadian blood pressure variations, a 24-hour pulse pressure (PP) and 24-hour mean blood pressure variability expressed in standard deviation (24MAP SD) and coefficient of variation (CV) were calculated.

Assessment of cognitive impairment

Cognitive impairment was assessed by using the following neuropsychological diagnostic tests: Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), and Montreal Assessment Cognitive Scale (MoCA). The MMSE is a 30-item questionnaire that examines functions including registration (repeating named prompts), recall, attention, orientation to time, language use, and the ability to follow simple commands. It is widely used to differentiate various types of dementias. The CDT is a valid complimentary tool to MMSE in the assessment of cognitive impairment severity. The MoCA is a 30-point test assessing multiple cognitive domains and is known as a sensitive tool for detecting mild cognitive impairments. MMSE 27–30, CDT ≥ 6, MoCA ≥ 26 scores were assumed as reference values corresponding to the norm.

Statistical analysis

Descriptive statistics included frequency distribution for categorical variables and means, standard deviation, and range for continuous variables. The Kolmogorov-Smirnov test, unpaired Student's t-test, Chi-square test, Spearman's rank correlation, and ANCOVA were used to compute differences between groups and to test the associations between study variables. Statistical analyses were performed using STATISTICA Version 12 (StatSoft Inc.).

Results

Baseline descriptive statistics are given in Table I. The mean age of the study group was 59.1 ± 6.1 years (mean ± SD). Mean BMI was 29.5 kg/m^2 but only 8 patients (19% of all cases) had BMI below 25.0 kg/m^2; the remaining were overweight or obese. Over half of them (64.3%) declared their education at least at the secondary level. There was a high prevalence of smokers (59.5%), and patients with dyslipidemia (57.1%) and abnormal glucose tolerance (30.9%). The total duration of HTN was 12.6 ± 11.2 years. Positive family history of hypertension was reported by 71.4% of respondents. Mean results of cognitive tests were within the normal range: 7.9 ± 2.0 scores in CDT and 27.6 ± 1.8 scores in MMSE. Only in the MoCA test, mean scores were below the reference range (24.9 ± 2.5 scores).

In the ABPM analysis, mean values of 24-hour systolic, diastolic and MAP pressure were 125.6 ± 13.5, 75.9 ± 9.8 and 92.9 ± 9.8 mm Hg, respectively (Table II). Dipping blood pressure profile was found in 37%, non-dipping in 61% and reverse-dipping in 2% of patients. Mean BPV was 12.2% which corresponded to 11.4 SD.

The results of neuropsychological tests were comparable between groups with normal and abnormal blood pressure profile (Table III). Among the analyzed BPV indicators, CV was inversely correlated with CDT ($r = –0.37$; $p = 0.03$) and MoCA ($r = –0.36$; $p = 0.02$), while SD was correlated only with CDT ($r = –0.41$; $p = 0.02$).

In multivariate analysis, after adjustment for including age, sex, education level and coexistence of abnormal lipid profiles (defined as the occurrence of at least one abnormality within LDL-cholesterol, HDL-cholesterol, and triglycerides levels), MoCA score was inversely associated with CV ($\beta = –0.41$; $p = 0.02$). Overall, males had significantly lower MoCA scores in comparison with females ($p = 0.03$) (Fig. 1).

Discussion

The relationship among hypertension and cognitive function is complex, albeit has not been fully

Table I. Clinical characteristic of the studied group. Data presented as means ± SD or percent; P-values for unpaired t-tests or chi-square test, respectively

	All n = 42	Females n = 24	Males n = 18	P-value ¶F vs. M
Anthropometrics:				
Age [years]	59.1 ± 6.1	60.1 ± 6.1	57.8 ± 6.1	0.24
Body mass index [kg/m^2]	29.8 ± 5.6	28.7 ± 4.3	31.2 ± 6.9	0.16
Office Blood Pressure:				
Systolic blood pressure [mm Hg]	147.2 ± 25.0	145.1 ± 20.3	149.7 ± 30.1	0.58
Diastolic blood pressure [mm Hg]	91.4 ± 12.9	88.1 ± 10.0	95.3 ± 15.0	0.08
Mean blood pressure [mm Hg]	110.0 ± 15.6	107.1 ± 11.7	113.4 ± 19.0	0.21
Laboratory tests:				
Fasting blood glucose [md/dL]	100.1 ± 18.1	99.4 ± 13.3	101.1 ± 23.6	0.76
Above 100 mg/dl (%)	31.0%	33.3%	27.8%	0.70
LDL-cholesterol [mg/dL]	112.1 ± 41.2	113.4 ± 45.8	110.5 ± 35.8	0.82
Above 100 mg/dl (%)	54.8%	54.2%	55.6%	0.93
HDL-cholesterol [mg/dL]	54.7 ± 18.8	60.2 ± 21.6	47.6 ± 11.6	0.03
Below 40 (males) or 45 (females) [mg/dl] (%)	33.3%	37.5%	27.8%	0.51
Triglycerides [mg/dL]	132.4 ± 63.0	144.8 ± 76.4	116.5 ± 35.9	0.15
Above 150 [mg/dl] (%)	31.0%	41.7%	16.7%	0.08
Medical history				
Hypertension duration [months]	12.6 ± 11.2	14.4 ± 12.0	10.3 ± 9.8	0.24
Smokers (%)	59.5%	62.5%	55.6%	0.65
Family history of hypertension (%)	71.4%	79.2%	61.1%	0.20
Primary education (%)	14.3%	12.5%	16.7%	0.70
Secondary education (%)	52.4%	62.5%	38.9%	0.13
Higher education (%)	33.3%	25.0%	44.4%	0.19
Neurocognitive tests:				
CDT [scores]	7.9 ± 2.0	8.0 ± 2.0	7.9 ± 2.1	0.85
MMSE [scores]	27.6 ± 1.8	27.8 ± 1.6	27.4 ± 2.1	0.44
MoCA [scores]	24.9 ± 2.5	25.5 ± 2.2	24.2 ± 2.7	0.08

CDT — Clock Drawing Test; MMSE — Mini-Mental State Examination; MoCA — Montreal Assessment Cognitive Scale

understood yet. An impact of midlife hypertension on the development of cognitive impairment has been recently extensively studied and there is growing evidence that elevated blood pressure is the most powerful among modifiable risk factors for cerebral vessel dysfunction that contribute to cognitive decline in later life [15, 31–36]. Numerous studies addressed this issue to specific blood pressure cut-offs, or more recently — exclusively to systolic blood pressure values [13, 14, 16, 31]. In this pilot study, we investigated a potential role of short-term blood pressure variations in cognitive impairments.

In clinical practice, ABPM is a method that allows not only to evaluate the effectiveness of antihypertensive therapy but also highly useful in predicting cardiovascular risk in patients with hypertension [37–41]. ABPM provides valuable information on the circadian variability of blood pressure and blood pressure patterns, which have been shown to be predictive for cognitive function [21, 42, 43]. Clinical studies in humans have demonstrated the strong association of cognitive impairment and VD with non-dipping, reverse-dipping and, extreme-dipping blood pressure patterns diagnosed by conventional 24-hour ABPM [22–25].

In our study, we found the presence of a non-dipping pattern in over 60% of patients. However, we did not find any differences in the neuropsychological test scores between the groups with normal and non-dipping pattern. A vast majority of studies

reporting such relationship suggested a potential role of secondary, hypertension-related the cerebral white matter lesions, higher frequency of lacunar infarction and reduction of total brain matter, which were strongly influenced by age [44–46]. In contrast to these reports, our study population was relatively younger and had no history of the symptomatic cerebrovascular disease. Furthermore, in contrast to the blood flow in other organs, cerebral blood flow increases during the night as a result of an increased oxygen demand [47]. Some authors suggest that in hypertensive patients a blunted reduction in nocturnal blood pressure may play an adaptive role in maintaining the night-time cerebral blood flow when autoregulatory mechanisms fail [48]. However, it seems unclear whether this adaptive mechanism is essential also in middle-aged patients without prior cerebrovascular events.

It has been well documented that aside from the conventional 24-h ABPM analysis, the ABPM indicators of short-term BPV may possess prognostic potential in the assessment of cerebrovascular risk [22, 26, 27, 49]. We found the scores in neuropsychological tests were inversely correlated with 24-h SD and CV. Bellelli et al. [49] demonstrated the association between cognitive decline and increased 24-hour BPV-CV in the elderly. They suggested that in hypertensive patients with the cognitive decline the sympathetic nervous system affects short--term BPV and its activation may be related to impaired baroreceptor response. Further studies are

Table II. Blood pressure values and circadian variability (24 hour ABPM)

Blood pressure	Mean (± SD)
24SBP [mm Hg]	125.6 ± 13.5
24DBP [mm Hg]	75.9 ± 9.8
24MAP [mm Hg]	92.9 ± 9.8
SBPd [mm Hg]	128.1 ± 14.2
DBPd [mm Hg]	78.3 ± 10.2
MAPd [mm Hg]	95.1 ± 10.3
SBPn [mm Hg]	118.1 ± 13.6
DBPn [mm Hg]	69.9 ± 8.8
MAPn [mm Hg]	87.1 ± 8.9
CV [%]	12.2 ± 3.1
24MAP SD [mm Hg]	11.4 ± 3.2
PP [mm Hg]	49.7 ± 9.1
Dippers (%)	36.6%
Non-dippers (%)	61.0%
Reverse-dippers (%)	2.4%

24SBP — 24-hour Systolic Blood Pressure; 24DBP — 24-hour Diastolic Blood Pressure; 24MAP— 24-hour Mean Blood Pressure; SBPd — Daytime Systolic Blood pressure; DBPd — Daytime Diastolic Blood Pressure; MAPd — Daytime Mean Blood Pressure; SBPn — Nocturnal Systolic Blood Pressure; DBPn — Nocturnal Diastolic Blood Pressure; MAPn — Nocturnal Mean Blood Pressure; CV — Coefficient of Variation; 24 MAP SD — 24-hour Mean Blood Pressure Variability Estimated by Standard Deviation; PP — pulse pressure

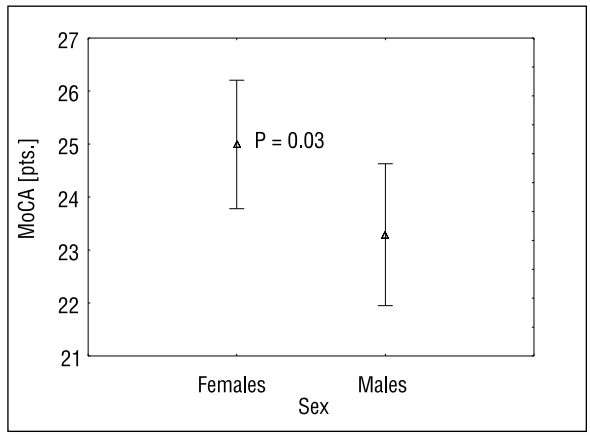

Figure 1. MoCA scores by gender adjusted for age — education level and lipid profiles

Table III. The relationship between blood pressure variability and pulse pressure with neuropsychological test scores

ABPM variable	Cognitive test	R	P-value
CV [%]	CDT	–0.37	0.03
	MMSE	–0.13	0.44
	MoCA	–0.36	0.02
24 MAP SD [mm Hg]	CDT	–0.40	0.02
	MMSE	–0.08	0.64
	MoCA	–0.27	0.09
PP [mm Hg]	CDT	0.02	0.91
	MMSE	0.06	0.73
	MoCA	0.13	0.41

CV — The Coefficient of Variation; 24MAP SD — 24-hour Mean Blood Pressure Variability (SD); PP — Pulse Pressure; CDT — Clock Drawing Test; MMSE — Mini-Mental State Examination; MoCA — Montreal Assessment Cognitive Scale; R — Spearman's Rank Correlation Coefficient

needed to elucidate whether this mechanism is also relevant in younger patients with uncomplicated hypertension.

We found significantly lower scores in the MoCA test in males in comparison to females. In the general population, cognitive decline is more common in women than in men. This is explained mostly by the longer life span [50–53] as well as an impact of genetics factors, sex hormone changes in midlife, and lower cognitive reserve that results in faster cognitive decline in women [50, 54, 55]. On the other hand, other studies demonstrated that compared with females, males showed significantly worse performance in Assessment Scale-cognitive subscale 13 (ADAS) evaluating subjective cognitive decline [56]. These gender discrepancies may be related to differences in cognitive domains evaluated by various neuropsychological tests. In this study, we used the MoCA scale, which is more specific for the assessment of memory, executive functions and psychomotor performance [57]. The MoCA scores are typically worse in the vascular cognitive decline associated with hypertension [58–60]. Our results seem consistent with earlier studies reporting that males have faster memory decline due to the typically earlier onset of cardiovascular disease, including primary hypertension [50, 61, 62].

Conclusions

In this a pilot-based study, mild cognitive impairment in middle-aged patients with long-lasting uncomplicated hypertension may be associated with increased diurnal variability of blood pressure.

Conflict of interest statement

The authors declare no conflict of interests.

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