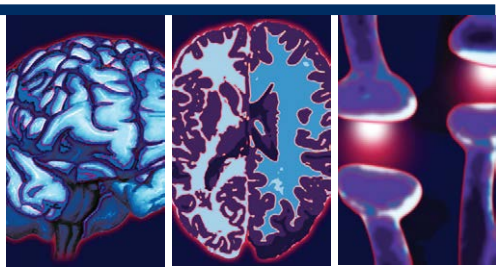

Low Diastolic Blood Pressure and High Blood Pressure Variability are Risk Factors for Cognitive Decline in Elderly Adults: A Case-Control Study

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ABSTRACT

Background

This study investigated the association between visit-to-visit blood pressure (BP) variability and cognitive decline in elderly adults over a 4-month period.

Methods

All 94 elderly volunteers were recruited from a community center. Mini-Mental Status Examination (MMSE) and Clinical Dementia Rating (CDR) questionnaires were administered during the initial assessment and at 4 months after the service. The BP at each visit and the visit-to-visit BP variability were measured for 4 consecutive months.

Results

The middle-stage/moderate cognitive impairment (MMSE scores ≤ 21) group exhibited significantly lower minimum diastolic BP and higher diastolic coefficient of variation values than did the mild/no cognitive impairment (MMSE scores >21) group did. After adjustment for the effects of age, the minimum diastolic BP was significantly and positively associated with the MMSE scores (P=0.033). To further evaluate the effects of low diastolic BP (LDBP) on cognitive function, we compared the initial and 4-month MMSE scores between the LDBP group (minimum diastolic BP ≤ 50 mmHg) and the control group (minimum diastolic BP>50 mmHg). We divided the volunteers into the following 4 groups: (1) hypertension history with LDBP (HT-c-LDBP), (2) hypertension history without LDBP (HT-s-LDBP), (3) no hypertension history without LDBP (nHT-s-LDBP), and (4) no hypertension history with LDBP (nHT-c-LDBP). The cognitive function differed significantly among the four groups (MMSE scores: HT-c-LDBP=21.62 ± 2.87; HT-s-LDBP=25.20 ± 2.78; nHT-s-LDBP=26.12 ± 3.65; and nHT-c-LDBP=23.27 ± 3.16). Compared to the nHT-s-LDBP group, the data showed that the HT-c-LDBP group exhibited significantly worse cognitive function, followed by the nHT-c-LDBP group.

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Conclusions

LDBP and high diastolic BP variability are risk factors for cognitive function decline in elderly adults.

Keywords

Diastolic blood pressure, Blood pressure variability, Cognitive decline, Elderly adults

Introduction

The relationship between blood pressure (BP) and dementia is not completely understood. Some studies have reported that hypertension is a risk factor for dementia and cognitive impairment [1-7]. By contrast, other studies have reported that diastolic hypotension is a risk factor [8]. However, some studies have reported the absence of association between BP and dementia development or cognitive decline over time in elderly adults [9,10]. Hypertension strongly affects cognitive decline in young adults, whereas persistent hypotension [8] or BP variability [11,12] strongly affects cognitive function in elderly adults. A prospective study involving 2505 Japanese–American men revealed that high systolic BP in middle age (average, 58 years) can be a predictor of senile dementia in late life (hazard ratio=1.77) [5]. Wang et al. reported that long-term hypertension causes microvascular injury, which consequently increases the risk of dementia in late life [13].

Mild cognitive impairment can be clinically defined as the earliest stage of dementia [14]. Both cognitive dysfunction [15] and hypertension [16] are common in elderly adults. The relationship between hypertension and cognitive decline has been widely studied. However, these studies have mainly focused on the effect of BP, as recorded during a single assessment, not as recorded during multiple measurements. The focus of these studies was not the effect of BP variability. The present study investigated the association between visit-to-visit BP variability and cognitive decline in elderly adults. This study was approved by the Institutional Review Board of the Taipei Tzu Chi Hospital (03-XD23-050), and all the participants provided written informed consent prior to participating in the study.

Methods

■ Inclusion criteria

The participants were adults aged ≥ 65 years who volunteered to participate in a community project between February 1, 2015, and July 31, 2015.

■ Inclusion procedure

After an explanation of the study objective, the volunteers were invited to participate in this study. Qualitative interviews were conducted by a trained senior nurse for obtaining basic information regarding the sex, age, medical history, and health behaviors (smoking, drinking, betel quid chewing, exercise, diet, and sleep) of the participants. All the information was verified by a geriatric psychiatrist.

■ Physical health

Height, body weight, body mass index, past history of hypertension, and BP at rest was measured at the index date. In addition, BP was measured in the morning one to five times every week for 4 consecutive months.

■ Cognitive function

The Mini-Mental State Examination (MMSE) is the most commonly used scale for the evaluation of cognitive function. It consists of a standardized six-domain cognitive screening test with a score range of 0-30. The MMSE items include questions for assessing orientation, registration and short-term recall memory, the ability to name objects, attention, and the ability to follow verbal and written commands, the ability to write a sentence, and visuospatial abilities while copying a figure. A total score <21 indicates increased odds of dementia [17,18].

The cut-off point of MMSE scores for low education levels are also indicated by a score of ≤ 21. In this study we defined a total MMSE score ≤ 21 as cognitive decline (middle-stage/moderate cognitive impairment [M/M CI]) and total scores MMSE >21 as noncognitive decline (mild/no cognitive impairment [M/N CI]) The MMSE and Clinical Dementia Rating (CDR; MMSE1 and CDR1) were administered during the initial assessment, and their updated versions (MMSE2 and CDR2) were administered 4 months after the initial evaluation.

■ Exclusion criteria

The participants were excluded if they (1) were unable to answer the questions asked by the interviewer because of illiteracy, (2) were unable to clearly hear the interviewer or communicate orally, (3) had received diagnoses of major physical or mental diseases, and (4) had an initial CDR scale score of ≥ 2.

■ Withdrawal criteria and rescue medication

The participants were permitted to withdraw from the study at any time during the study period. The primary investigator provided transfer assistance for rescue medication to all the participants who experienced symptom deterioration and required immediate medical assistance.

■ Assessment protocol

BP was self-measured by each participant by using a cloud-computing sphygmomanometer prior to participation in voluntary activities at the community center. The participants were instructed to use the following standard protocol to measure BP: (1) rest for 15 min, (2) swipe an individual cloud card, (3) place the right arm through the measuring tunnel, (4) press the start key to start BP measurement, and (5) write down the values of BP and heart rate. In addition, BP was measured prior to participation in each voluntary activity for 4 consecutive months. At the end of the 4-month data-collection period, the principal investigator calculated the maximum systolic BP and systolic coefficients of variation (CVs) as well as the minimum diastolic BP and diastolic CVs.

■ Statistical analysis

The participants were divided into two groups, namely the M/M CI (MMSE ≤ 21) and M/N CI (MMSE >21) groups for comparing their basic data and determining the statistical significance of the variations between the initial cognitive indexes. Furthermore, we redivided all the participants into the following four groups: (1) hypertension history with LDBP (HT-c-LDBP), (2) hypertension history without LDBP (HT-s-LDBP), (3) no hypertension history without LDBP (nHT-s-LDBP), and (4) no hypertension history with LDBP (nHT-c-LDBP) to test the associations among hypertension history, visit-to-visit variation in diastolic BP, and cognitive function.

Results

Of the 94 participants who were originally recruited, 82 completed the initial cognitive function assessment. All these participants were volunteers from the community center; 29.3% of all the participants had a past history of hypertension; and 20 participants exhibited diastolic BP <50 mmHg in the 4 months of the study, of which 55% had a history of hypertension. The mean values of systolic (122.2 ± 10.5 mmHg) and diastolic (60.0 ± 5.7 mmHg) BP in the LDBP group were lower than those in the control group (134.7 ± 12.2 mmHg and 72.3 ± 8.6 mmHg). Furthermore, 29.8% of the participants with hypertension history consumed anti-hypertension drugs. The percentages of participants with a history of diabetes and of hyperlipidemia but not stroke were 8.5% and 4.9%, respectively.

Of the participants, 19 participants who had MMSE scores ≤ 21 were assigned to the M/M CI group and 63 participants with MMSE scores >21 were assigned to the M/N CI group. BP measurements were obtained 22.9 times during the 4-month period on average. The basic data did not differ significantly between the M/M CI and M/N CI groups, except for age and education level **(Table 1)**. As illustrated in **Table 2**, the participants in the M/M CI group exhibited significantly lower minimum diastolic BP and higher diastolic CV than did those in the M/N CI group.

A linear regression model was developed using the MMSE scores obtained after 4 months as the dependent variable and age and minimum diastolic BP as independent variables. The results revealed that after adjustment for the effect of age, the minimum diastolic BP was significantly and positively associated with MMSE scores (MMSE=−0.175 × age + 0.082 × minimum diastolic BP + 33.49; P=0.033; **Table 3**).

To further evaluate the effects of low diastolic BP (LDBP) on cognitive function, we used the quartile of minimum diastolic BP to assign 25% of the participants with LDBP (≤ 50 mmHg) to the LDBP group and those with relatively high diastolic BP (>50 mmHg) to the control group. According to their history of hypertension, we divided all the participants into four groups, namely HT-c-LDBP, HT-s-LDBP, nHT-s-LDBP, and nHT-c-LDBP. The associations between hypertension history, visit-to-visit LDBP, and cognitive function were tested. A positive correlation was observed between

Table 1: Difference in demographic characteristics between participants with mild/no cognitive impairment and middle-stage/moderate cognitive impairment.

Variable	Group	Number (N=82)	Average	SD	t	Significance
MMSE score	M/N CI[a]	63	25.98	2.54	12.03	<0.01
	M/M CI[b]	19	19.26	2.00		
Age	M/N CI	63	73.68	5.875	-3.684	<0.01
	M/M CI	19	79.47	6.441		
Sex	M/N CI	63	Female:47	Male:16	X2=1.84	NS
	M/M CI	19	Female:17	Male:02		
HTN	M/N CI	62	19 (30.6%)		X2=0.78	NS
	M/M CI	19	5 (26.3%)			
Anti HTN drug	M/N CI	62	20 (31.7%)		X2=0.78	NS
	M/M CI	19	5(26.3%)			
Waist Circumference	M/N CI	62	86.31	9.735	-1.589	NS
	M/M CI	18	90.36	8.665		
Systolic pressure	M/N CI	60	125.98	16.324	-1.541	NS
	M/M CI	18	132.72	16.117		
Diastolic pressure	M/N CI	60	65.37	11.701	.101	NS
	M/M CI	18	65.11	8.547		
Heart rate	M/N CI	60	74.80	12.565	-2.076	0.041
	M/M CI	18	81.44	9.275		
BMI	M/N CI	63	23.7998	3.38386	-1.963	NS
	M/M CI	19	25.4645	2.68816		
Numbers of BP check	M/N CI	63	24.62	22.50	-0.647	NS
	M/M CI	19	28.47	23.65		

[a]M/N CI: mild/no cognitive impairment
[b]M/M CI: middle-stage/moderate cognitive impairment

Table 2: Differences in blood pressure and blood pressure variability between participants with mild/no cognitive impairment (M/N CI)[a] and middle-stage/moderate cognitive impairment (M/M CI)[b].

Group		n	Average	SD	t test equivalent to average				
					t	DF	Significance	95% CI of the Difference	
								Lower limit	Upper limit
Max SBP[c]	M/N CI	54	157.96	18.20	-1.56	68.00	n.s	-17.34	2.14
	M/M CI	16	165.56	12.76					
Sys CV[d]	M/N CI	50	10.03	3.37	-0.77	64.00	n.s	-2.64	1.17
	M/M CI	16	10.76	3.17					
Min DBP[e]	M/N CI	55	58.56	13.06	2.43	69.00	0.02	1.48	15.15
	M/M CI	16	50.25	7.47					
Dia CV[f]	M/N CI	50	10.88	4.33	-2.16	64.00	0.03	-5.32	-0.20
	M/M CI	16	13.65	4.86					

[a]M/N CI: mild/no cognitive impairment
[b]M/M CI: middle-stage/moderate cognitive impairment
[c]Max SBP: maximum systolic blood pressure
[e]Min DBP: minimum diastolic blood pressure
[d]Sys CV: systolic coefficient of variation
[f]Dia CV: diastolic coefficient of variation

MMSE scores and the minimal systolic and diastolic BP values. The four groups differed significantly in cognitive function (MMSE scores: HT-c-LDBP=21.62 ± 2.87; HT-s-LDBP=25.20 ± 2.78; nHT-s-LDBP=26.12 ± 3.65; and nHT-c-LDBP=23.27 ± 3.16) (Table 4). The HT-c-LDBP group, followed by the nHT-c-LDBP group, had significantly worse cognitive function than the nHT-s-LDBP group did. In other words, low minimum diastolic BP may be a risk factor for cognitive decline, particularly in patients with any past history of hypertension. The participants with hypotension and without any history of hypertension were

Table 3: Linear regression model for Mini-Mental Status Examination score, minimum diastolic pressure, and age.

Coefficients[a]					
Model	**Unstandardized coefficients**		**Standardized coefficients**	**t**	**Sig.**
	B	**Std. error**	**Beta**		
(Constant)	33.494	6.432		5.207	0.000
Min DBP[b]	0.082	0.037	0.281	2.192	0.033
Age	-0.175	0.070	-0.321	-2.503	0.015

[a]Dependent Variable: Mini-Mental Status Examination (MMSE) score

[b]Min DBP: Minimum diastolic blood pressure

Table 4: Comparing the difference of the initial and final Mini-Mental Status Examination scores among the nHT-c-LDBP, nHT-s-LDBP, HT-c-LDBP, and HT-s-LDBP groups by the method of ANOVA.

		N	**Mean**	**S.D.**	**95% C.I**		**df**	**F**	**p-value**
					Law limit	**Upper limit**			
MMSE01	nHT-c-LDBP	11	23.1818	3.57262	20.7817	25.5819	3	0.898	0.447
	nHT-s-LDBP	35	24.6286	3.57348	23.4010	25.8561	1		
	HT-c-LDBP	9	23.6667	4.00000	20.5920	26.7413	1		
	HT-s-LDBP	15	25.2000	2.78260	23.6590	26.7410	2		
MMSE02	nHT-c-LDBP	11	23.2727	3.16515	21.1463	25.3991	3	4.958	0.004
	nHT-s-LDBP	25	26.1200	3.65513	24.6112	27.6288	1		
	HT-c-LDBP	8	21.6250	2.87539	19.2211	24.0289	1		
	HT-s-LDBP	14	25.5714	2.70937	24.0071	27.1358	2		

Post hoc LSD test of multiple comparison: HT-c-LDBP< nHT-c-LDBP < nHT-s-LDBP P<0.05

LDBP: Low Diastolic Blood Pressure (The minimum diastolic pressure ≤ 50 mmHg **in recent four months). nHT: no past hypertension history.** Mini-Mental Status Examination (MMSE01): Initial assessment MMSE score. MMSE02: MMSE score after 4 months of the voluntary activity program.

also at a risk of cognitive decline, particularly if the minimum diastolic BP was ≤ 50 mmHg during the 4-month assessment of visit-to-visit BP variability.

Discussion

The results of this study revealed that LDBP and high diastolic BP variability are risk factors for cognitive function decline in elderly adults. In addition, our data demonstrated that hypertension is not a predictor of cognitive decline in adults aged >65 years. This finding is consistent with the results of other studies that have reported no significant relationship between hypertension and cognitive impairment among certain populations [8] or in women in late life [19]. A prospective horizontal study including 9704 women reported a strong association between hypertension and cognitive function decline in patients with incident stroke (odds ratio [OR]=4.07; 95% confidence interval [CI]=1.37–12.1) but not in patients without stroke (OR=1.13; 95% CI=1.04–1.22). Our recruited participants were all aged >65 years and without any stroke history. In this study, we attempted to test the relationship between cognitive function decline and visit-to-visit BP variability. The results showed that cognitive function was not significantly correlated with mean or maximum systolic and diastolic visit-to-visit BP variability. A significant correlation was observed among MMSE scores, the minimum systolic BP (r=0.386, P<0.001), and the minimum diastolic BP (r=0.476, P<0.001). Furthermore, this correlation was still present after controlling for the current use of antihypertensive drugs. The results indicated that low BP may be a risk factor for cognitive decline in elderly adults. In this study, a 4-month history of LDBP (<50 mmHg) was associated with cognitive function decline.

All the elderly adults recruited for the study mainly visited the community center for participating in voluntary resource recycling activities. The cognitive function may have improved during their daily voluntary activities and active social interaction. Therefore, that the control group was expected to exhibit improved cognitive function persistently for 4 months (the duration of the voluntary activity program). The MMSE scores of control group showed a slight increase (from 25.07 ± 3.1 to 25.92 ± 3.3) after 4 months, but a slight decrease was observed in the scores of the LDBP group (from 23.26 ± 3.7 to 22.57 ± 3.1). This may be related to poor blood circulation to the brain in the LDBP group. Therefore, we should consider increasing voluntary activities in exercise and reducing durations of sedentary

activities for improving the blood circulation to the brain as well as alleviating hypotension and BP variability. In summary, we did not observe a correlation between hypertension and cognitive decline. However, variations in hypotension (diastolic BP variability) and minimum diastolic BP are more likely to be associated with cognitive deficits in elderly adults.

den Heijer [20] reported that cerebrovascular diseases can induce a pattern of brain tissue atrophy, a characteristic observed in patients with Alzheimer disease. Furthermore, on the basis of magnetic resonance images, the aforementioned study reported that a 5-year history of untreated hypertension can be a predictor of hippocampal atrophy, and a 5-year history of persistent LDBP in patients receiving hypertensive agents was associated with atrophy of the amygdala and hippocampus [20]. In addition, other studies have reported that high BP variability, which was calculated using multiple one-time measurements but not from average BP measurements, might be related to the shrinkage of the hippocampus [21]. Therefore, that study suggested that the initial effect of high BP on cognitive function occurred before the age of 65 years. After more than a decade of the effect, LDBP and high BP variability may reflect the effects of insufficient blood perfusion on cognitive decline in elderly adults.

Brain imaging was not performed in this study. Nevertheless, by measuring variations in MMSE scores, we demonstrated an association between short-term untreated diastolic hypotension and cognitive function decline. The cause of extreme LDBP remains unclear. However, in addition to physical factors, LDBP may be caused by an increased risk of multi vessel infarction or by progressive changes in the regional brain blood circulation caused by long-term hypertension, including increased blood viscosity and severe vascular sclerosis. Additional detailed assessments should be conducted in patients with extreme LDBP. Necessary adjustments should be made regarding individual health education for preventing cognitive function deterioration. Different preventive measures should be developed to control hypotension, particularly in patients with any past history of hypertension and large variability in diastolic BP.

Limitations

This study has some limitations. First, all the participants were recruited from a single community center, and none of them had received a clinical diagnosis of dementia. Thus, generalizing the results to other populations is difficult. Second, the sample size of the study was small, and the follow-up period was only 4 months. Third, we used qualitative measures rather than imaging studies to evaluate changes in cognition. Additional studies with a larger sample sizes and a longer follow-up periods than the current study as well as studies using cerebral imaging examinations are required to validate our finding that diastolic hypotension significantly influences cognitive function decline.

Conclusions

Our study results revealed an association between cognitive decline and LDBP and that between cognitive decline and high visit-to-visit BP variability in elderly adults. These findings may indicate the effects of cerebral perfusion on cognitive impairment in elderly adults. Additional studies with a prospective follow-up design are warranted to explore the mechanisms underlying the effects of LDBP and high BP variability on cognitive function.

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Conflict of Interest

The authors declare there is no conflict of interest.

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