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The relationship between blood pressure and cognitive function

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ABSTRACT

Background: Although an elevated systolic blood pressure (SBP) is associated with cognitive dysfunction, BP may decrease with advanced cognitive dysfunction; therefore, we attempted to identify the turning point in the relationship between cognitive function and SBP in elderly subjects.
Methods: In pooled datasets of general populations and outpatient clinics (age>65 years), in which the risk of frailty or cognitive dysfunction was assessed (N = 4076), the relationship between SBP and the Mini Mental State Examination (MMSE) score was examined.
Results: Mean age was 72.5 ± 6.2 years (male 45.1%), and SBP was 133.0 ± 19.5 mmHg. In an analysis of locally weighted scatter plot smoothing, the relationship between SBP and MMSE scores changed at an MMSE score of 24 points. In subjects with preserved cognitive function (MMSE ≥24 points), MMSE scores decreased with increases in SBP (B = −0.047 per 10 mmHg increase, P = 0.002) after adjustments for age, sex, body mass index, alcohol habit, smoking status, diabetes, a history of stroke, and the geriatric nutritional index; however, in subjects with reduced cognitive function (MMSE<24 points), decreases in the MMSE score were associated with reductions in SBP (B = 1.178 per 1 point decrease in the MMSE score, P = 0.002).
Conclusion: The relationship between SBP and cognitive function changed at a MMSE score of approximately 24 points (mild to moderate cognitive dysfunction). In patients with preserved MMSE, higher BP values were associated with a reduction of cognitive function, but this was not a case for those with impaired MMSE.

1. Introduction

The severity of hypertension is associated with cognitive impairment [1]. The administration of antihypertensive medications and intensive blood pressure (BP) lowering to systolic BP (SBP) < 120 mmHg in automated office BP measurements were shown to attenuate both cognitive decline and the development of dementia [2]. A systematic review and meta-analysis of combined clinical trial data confirmed significant reductions in the risk of cognitive decline and the development of dementia with the administration of antihypertensive medications [3]. In clinical trials that examined the preventive effects of antihypertensive medication against the deterioration of cognitive function, subjects with dementia at baseline were excluded prior to the initiation of these trials [3].

In contrast, lower BP in later life under antihypertensive medication has been associated with the worsening of dementia and higher mortality rates [4]. The relationship between lower BP and reduced cognitive dysfunction may be attributed to a worsening nutritional status [5], reduced physical activities [6], and comorbidities in the elderly population. Therefore, the causal relationship appears to change at a certain threshold of cognitive dysfunction. In the clinical management of BP in elderly subjects, the level of cognitive function that alters the BP management strategy from intensive BP lowering needs to be identified in order to avoid excessive BP lowering.

Therefore, the purpose of the present study was to clarify the turning point in cognitive function that alters its relationship with BP.

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2. Methods

2.1. Subjects

Data of 6530 elderly subjects aged over 65 years was pooled from the general Japanese populations (Kusatsu, N = 2021; Hatoyama, N = 724; Yoita, N = 637; Nangai, N = 1418; Takashimadaira, N = 1248) and from outpatients' clinic to evaluate frailty in Tokyo Metropolitan Geriatric Hospital (N = 482). Detail of subjects enrolled in each general population are published previously [7,8]. The details of frail outpatients' clinic was also reported previously [8]. Subjects with cardiometabolic disease such as diabetes, dyslipidemia, hypertension, atrial fibrillation, and heart failure, and those who had suspected of having frailty from complaints of memory loss, reduced waking speed, fatigue, vertigo, appetite loss, and body weight loss was enrolled in the frail outpatients' clinic. The subjects with known history of severe dementia, untreated malignancy, and severe mental disease were excluded. In the present study, we could evaluate 4794 subject's data in this pooled analysis after excluding subjects with missing MMSE score.

2.2. Measurement of BP and cognitive function

In 5 Japanese general population (Kusatsu, Hatoyama, Yoita, Nangai, and Takashimadaira) systolic and diastolic blood pressures (SBP and DBP) were measured twice on the right arm by trained nurses using an automatic blood pressure monitoring device with the oscillometric method after a 5-min rest. In frail outpatients' clinic, clinic BP was measured twice in right upper arm using semiautomated clinic BP device (BP-900, Fukuda Colin, Japan) in the sequence of the right-left-right-left upper arm after 5 min rest. Each BP data was printed out automatically in a sheet of paper after the measurement, and the subjects brought the BP results to the physician or nurses. We used data of mean of two BP readings on the right arm in this analysis.

Cognitive function was evaluated using Mini Mental State Examination (MMSE) [9] by trained clinical psychologists. Nutritional status was evaluated using geriatric nutritional index [GNRI = (14.89 × albumin) + 41.7 × (body weight/Ideal body weight)] [10].

2.3. Informed consent

The internal review board of the Tokyo Metropolitan Geriatric Hospital approved each study, and written informed consent for the studies were obtained from each individual. The pooled analysis and submission of the present paper was approved by the internal review board (R20-48).

2.4. Statistical analysis

Data are shown as mean ± SD or percentage values. Relationship between BP and MMSE score was evaluated in scatter plotting and locally weighted scatter plots smooth (LOESS) was applied to evaluate the point changing the relationship. In subjects less than and above the threshold MMSE score, linear relationship between BP and MMSE score was evaluated using Pearson's correlation. Multiple linear regression analysis was performed to exclude the effect of confounding factors of age, sex, body mass index, alcohol drinking habit, smoking status, diabetes, history of stroke and GNRI.

In order to evaluate BP levels associated with reduced MMSE score, we stratified the subjects according to their SBP level (i.e. <110, 110–119, 120–129, 130–139, 140–149, ≥150 mmHg). One-way analysis of variance was performed to evaluate the difference in continuous variables among BP groups and Tukey's honestly significant difference test was performed to evaluate the intergroup difference. The chi-square test was used to detect differences in the frequencies of characteristics between the groups. Analysis of covariance (ANCOVA) was performed to evaluated the difference in continuous variables among BP groups after adjustment for confounding factors and Bonferroni test was performed to evaluate the intergroup difference. *P*-values of <0.05 were considered to be statistically significant. The statistical software IBM-SPSS (version 25.0) was used for all analyses.

3. Results

3.1. Subjects

The characteristics of the total subjects are shown in Table 1. At the baseline, the subjects' mean age was 74.2 ± 6.2 years, 47.3% of the subjects were males.

3.2. Relationship between BP and MMSE score

Scatter plots and LOESS curve of MMSE score to SBP and DBP are shown in Fig. 1. MMSE score decreased with an increase of SBP in subjects with MMSE score ≥24 points, while SBP decreased with a decrease of MMSE score in those with MMSE<24 points. Characteristics of subjects with MMSE score <24 points and MMSE ≥24 points are shown in Table 1. Subjects with MMSE score ≥24 points were younger, had less antihypertensive medication, higher GNRI, and higher serum albumin. In subjects with MMSE ≥24 points, MMSE score was significantly and inversely related to SBP ($r = -0.069$, $p < 0.001$) and the relationship remained significant even after adjustment for confounding factors in multiple linear regression analysis (B = −0.047 per 10 mmHg increase, 95% confidence interval −0.077 to −0.017, P = 0.002) (Table 2). In subjects with MMSE <24 points, SBP was significantly and positively related to MMSE score ($r = 0.179$, $P < 0.001$) and the relationship remained significant even after adjustment for confounding factors (B = 1.178, 95%CI 0.447 to 1.909, P = 0.002) (Table 3).

Scatter plots and LOESS curve between pulse pressure to MMSE score

Table 1
Characteristics of subjects.

	Total	MMSE		P
		<24	≥24	
N	4794	425	4369	
Age, years	74.2 ± 6.2	78.3 ± 7.0	73.8 ± 6.0	<0.001
Male, %	47.3	44.7	43.6	0.655
Body mass index, kg/m2	23.2 ± 3.2	22.9 ± 3.5	23.2 ± 3.2	0.121
Systolic BP, mmHg	132.8 ± 20.0	134.2 ± 21.7	132.7 ± 19.8	0.138
Diastolic BP, mmHg	75.0 ± 12.0	74.3 ± 13.0	75.1 ± 11.9	0.246
Pulse pressure, mmHg	57.8 ± 14.0	60.0 ± 14.9	57.6 ± 13.9	0.001
Mean BP, mmHg	94.3 ± 13.6	94.3 ± 14.8	94.3 ± 13.5	0.976
Smoking status				0.978
Current smokers, %	12.1	12.6	12.3	
Past smokers, %	27.7	27.6	28.3	
Regular alcohol drinkers	43.5	31.8	45.8	<0.001
Hypertension, %	45.5	58.0	49.0	0.001
Antihypertensive medication, %	62.0	67.9	55.0	<0.001
Diabetes, %	16.3	21.7	17.5	0.037
History of stroke, %	6.5	9.1	7.0	0.121
History of heart disease, %	7.2	9.3	7.8	0.286
GNRI	107 ± 8	105 ± 8	107 ± 8	<0.001
Albumin, mg/dl	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.3	<0.001
Total cholesterol, mg/dl	205.7 ± 36.0	199.9 ± 38.3	206.2 ± 35.7	0.001
Triglyceride, mg/dl	146.4 ± 88.8	147.2 ± 89.5	138.9 ± 81.8	0.074
HDL cholesterol, mg/dl	61.4 ± 16.1	59.1 ± 16.4	61.6 ± 16.1	0.002
HbA1c, %	5.6 ± 0.9	5.7 ± 1.1	5.6 ± 0.8	0.026

P values were calculated using non-paired *t*-test or chi-square test between subjects with MMSE <24 and ≥ 24.

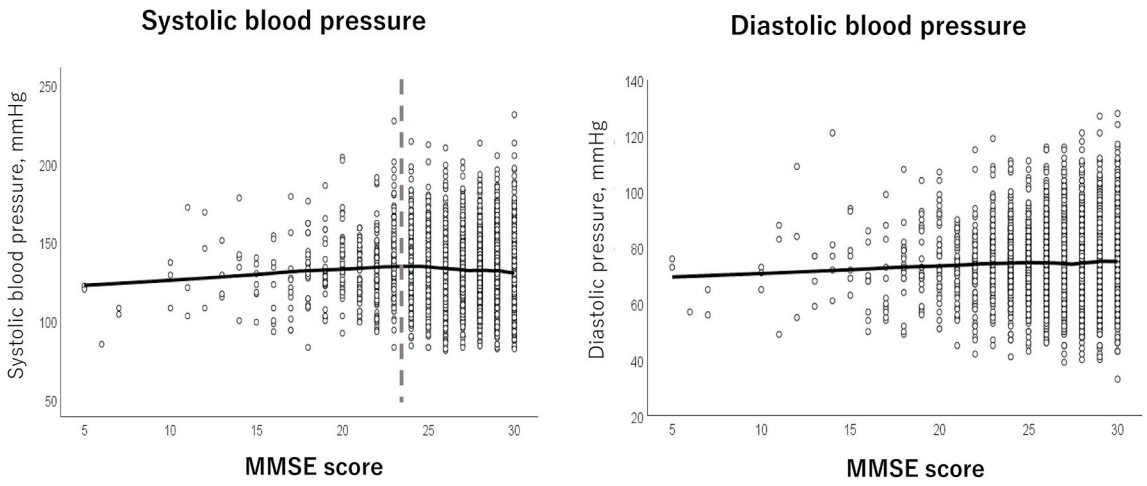

Fig. 1. Scatter plots and LOESS curve of MMSE score to SBP and DBP.

Table 2
Multiple linear regression analysis for MMSE in subjects with MMSE ≥24.

	Unstandardized B	Standardized beta	95% CI		P
Systolic blood pressure, per 10 mmHg	−0.047	−0.050	−0.077	−0.017	0.002
Age, years	−0.061	−0.199	−0.072	−0.051	<0.001
Sex、men = 1, women = 2	0.152	0.041	0.026	0.277	0.018
Body mass index, kg/m2	0.002	0.004	−0.028	0.032	0.882
Regular alcohol drinking habit, no = 0, yes = 1	0.259	0.070	0.134	0.384	<0.001
Smoking status, current = 1, past = 2, non = 3	−0.003	−0.028	−0.007	0.00000	0.076
Hypertension, no = 0, yes = 1	0.005	0.001	−0.116	0.127	0.930
Diabetes, no = 0, yes = 1	0.016	0.003	−0.137	0.170	0.835
History of stroke, no = 0, yes = 1	−0.138	−0.019	−0.365	0.088	0.231
History of heart disease, no = 0, yes = 1	0.200	0.029	−0.021	0.420	0.077
GNRI, 1 point	−0.006	−0.025	−0.018	0.006	0.351

P values were calculated using multiple linear regression analysis. GNRI, geriatric nutritional index.

Table 3
Multiple linear regression analysis for systolic blood pressure in subjects with MMSE <24.

	Unstandardized B	Standardized beta	95% CI		P
MMSE, 1 point	1.178	0.166	0.447	1.909	0.002
Age, years	0.189	0.057	−0.161	0.539	0.289
Sex, men = 1, women = 2	1.579	0.036	−3.700	6.858	0.557
Body mass index, kg/m2	−0.045	−0.007	−1.256	1.166	0.941
Regular alcohol drinking habit, non = 0, yes = 1	1.548	0.034	−3.659	6.754	0.559
Smoking status, current = 1, past = 2, non = 3	−0.063	−0.002	−3.682	3.556	0.973
Hypertension, no = 0, yes = 1	0.836	0.019	−3.890	5.563	0.728
Diabetes, no = 0, yes = 1	−4.858	−0.092	−10.422	0.706	0.087
History of stroke, no = 0, yes = 1	0.494	0.007	−7.062	8.050	0.898
History of heart disease, no = 0, yes = 1	−5.457	−0.072	−13.273	2.359	0.171
GNRI, 1 point	0.380	0.145	−0.127	0.886	0.141

P values were calculated using multiple linear regression analysis. GNRI, geriatric nutritional index.

is shown online supplemental file (Fig. S1). The relationship was changed at the point of MMSE score of 24 points, similar to the result of SBP. The results of multiple linear regression analysis for pulse pressure are also shown in online supplemental file (Tables S1 and S2). In subjects with MMSE score ≥24 points, MMSE score was significantly and inversely associated to pulse pressure (B = − 0.010 per 1 mmHg increase, 95% CI -0.015 to −0.006, P < 0.001), and in those with MMSE score < 24 points, the lower pulse pressure was associated with the lower MMSE score (B = 1.160 per MMSE 1 point, 95% CI 0.673 to 1.647, P < 0.001), in the parallel multiple linear regression analysis.

MMSE score linearly decreased with a decreased DBP in total subjects (Fig. 1) (r = 0.033, P = 0.023), but the relationship was disappeared after adjustment for age and sex in multiple linear regression analysis (B = −0.002, 95%CI -0.009 to 0.006, P = 0.672).

3.3. SBP level to have a decreased MMSE score

We stratified the subjects according to SBP levels to have a decreased MMSE score in subjects with MMSE score ≥24 points and in those with MMSE score <24 points. The characteristics of subjects with each SBP group in subjects with MMSE score ≥24 points are shown in Table S3. The subjects with SBP≥150 mmHg had a significantly lower MMSE score than those with SBP<110 mmHg, and those with SBP 110–119 mmHg. Even after adjustment for confounding factors, subjects with >150 mmHg had a significantly lower MMSE score than those with SBP <110 mmHg (Fig. S2).

The characteristics of subjects stratified SBP groups in subjects with MMSE score <24 points, are shown in Table S4. The subjects with SBP <110 mmHg had a significantly lower MMSE score, compared to the

other all subjects' groups. The significance in lower MMSE score levels in subjects with SBP <110 mmHg group remained even after adjustment confounding factors (Fig. S3).

Relationship between SBP and MMSE score in subjects with and without antihypertensive medication.

Among 3395 subjects whose data of antihypertensive medication use was available, 62.0% of subjects (N = 2106) were taking antihypertensive medication. Scatter plots between MMSE score and SBP in subjects with and without antihypertensive medication use are shown in online supplemental file (Fig. S4). There was no certain threshold of MMSE score in the LOESS curve. In the parallel analysis which was performed separately in subjects with and without antihypertensive medication use, the results between SBP and MMSE were similar, but lost the statistical significance (Tables S5, S6, S7, and S8): MMSE score was significantly associated to GNRI, BMI, and smoking status in subject with MMSE score ≥ 24 points and without antihypertensive medication use.

4. Discussion

The relationship between SBP and cognitive function changed at a MMSE score of approximately 24 points (mild to moderate cognitive dysfunction). This score was previously reported to discriminate Alzheimer-type dementia from mild cognitive impairment with a sensitivity of 68.7% and specificity of 78.8% [11].

It was reported that higher SBP in mid-life and lower SBP in late-life were associated with an increased risk of developing dementia in a 32-year prospective study, but no certain turning point of changing relationship between chronological age and dementia was mentioned [12]. Ryuno et al. [5] higher SBP was associated with cognitive dysfunction in elderly subjects with 70 years old, but not in those with 80 years old in the general population; therefore, age between 70 and 80 years old seemed to be the threshold of changing the relationship between SBP and cognitive dysfunction. However, in our study, it was difficult to find out certain age to change the relationship. Levels of physical activity in daily life, and biological ageing might be a possible indicator of changing the relationship between SBP and cognitive dysfunction, and further study will be required.

In subjects with preserved cognitive function, SBP >150 mmHg correlated with a lower MMSE score. Intensive SBP lowering has been suggested to more effectively prevent the development of dementia [2]. In elderly patients with SBP >150 mmHg, clinicians need to control BP at 130 mmHg even in subjects with frailty. Intensive SBP lowering has been shown to reduce the progression of deep white matter lesions [13], the cerebrovascular cause of dementia. In a systematic review and meta-analysis, significant reductions in the risk of cognitive decline and the development of dementia were observed with the administration of antihypertensive medications [3]. Cognitive dysfunction may be caused by cerebrovascular diseases and the Alzheimer's pathology (i.e. the deposition of amyloid β and tau). Antihypertensive medication was also shown to influence the metabolism of amyloid β [14]. A previous study demonstrated that the treatment of hypertension with nilvadipine, a calcium channel blocker, promoted cerebral blood flow in the hippocampus [15].

Among subjects with cognitive dysfunction and MMSE <24 points in the present study, those with SBP <110 mmHg had a lower MMSE score. SBP <110 mmHg under antihypertensive medication has been associated with worsening cognitive function in elderly subjects with mild cognitive impairment or mild dementia [16]. The elderly subjects with cognitive dysfunction might be considered withdrawal of antihypertensive drug in those with SBP <110 mmHg; however, the discontinuation of antihypertensive medication did not prevent cognitive dysfunction in a previous study [17]. This was possibly because of reversed causality. Nutritional dysfunction and low BMI [18] caused by sarcopenia and cachexia may contribute to the relationship observed between a low MMSE score and low SBP [5]. Body weight loss may also increase the risk of the progression of cognitive impairment and the development of dementia [19]. Changes in food preferences attributable to the progression of cognitive dysfunction may result in body weight loss and the lowering of BP [19].

The present study had the following limitations [1]: Data on antihypertensive medication and years of education were unavailable in many subjects [2]. Some subjects had a history of stroke and heart disease [3]. In the cross-sectional study, difficulties were associated with demonstrating the causal relationship between BP and MMSE and, thus, a longitudinal study is required in the future [4]. Only a few subjects had MMSE <24 points, and differences in MMSE scores between BP groups were also small [7]. Subjects with cognitive dysfunction and a low quality of life were more likely to show greater variabilities in BP [20, 21].

5. Conclusion

The relationship between SBP and cognitive function changed at a MMSE score of approximately 24 points (mild to moderate cognitive dysfunction). In patients with preserved MMSE, higher BP values were associated with a reduction of cognitive function, but this was not a case for those with impaired MMSE.

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Disclosure

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2021.200104.

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