Cognitive Impairment and Nocturnal Blood Pressure Fall in Treated Elderly Hypertensives

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Abstract

Objectives: We investigated the association between the fall of nocturnal blood pressure (BP) and cognitive impairment in elderly subjects.

Methods: The study was a cross-sectional survey of 204 elderly subjects who had no cerebrovascular episodes. Ambulatory BP monitoring and assessments of cognitive functions using the Mini-Mental State Examination (MMSE) were performed at the subjects' homes. We classified the subjects treated with antihypertensive drugs into three groups: non-dippers (nocturnal fall <10% of the mean day diastolic BP; n=51), normal dippers (10% to less than 20%; n=58), and extreme dippers (20% or more; n=17). The subjects not treated with antihypertensive drugs were also classified as non-dippers (n=40), normal dippers (n=24), and extreme dippers (n=14).

Results: The mean age of participants was 75.2±7.2 years, and 126 (61.7%) were being treated with antihypertensive drugs. In the group of antihypertensive drug users, the number with MMSE≤23 was 30 and the adjusted odds ratio for cognitive impairment in those with an extreme dip in diastolic BP (DBP) was 4.18 (95% CI, 1.07–16.40) in reference to the normal dippers. In contrast, no association was observed between cognitive function and nocturnal BP fall in the group not using antihypertensive drugs.

Conclusions: Cognitive impairment was associated with an extreme dip in DBP in the antihypertensive drug users only. It remains to be seen whether careful monitoring of nighttime BP as well as daytime BP may reduce the risk of cognitive impairment in antihypertensive drug users.

Key words: cognitive function, nocturnal blood pressure fall, elderly in the community, antihypertensive treatment, ambulatory blood pressure monitoring

Introduction

Some studies reported that patients diagnosed as hypertensive have shown lower scores in cognitive performance tasks in comparison with normotensive controls (1, 2). Considerable controversy exists, however, as to the relationship between blood pressure (BP) and cognitive performance in the general elderly population in cross-sectional studies (3–7) and in longitudinal investigations (8–10); in the Framingham study (8), Elias et al. reviewed that elevated BP measured 20 years earlier was inversely associated with subsequent performance in a

variety of cognitive tests in subjects never treated for hypertension.; a report from the Honolulu-Asia Aging Study (9) found that a systolic BP (SBP) of less than 110 mmHg was cross-sectionally related to poor cognitive function in men aged 74–93 years, although increased midlife systolic BP was a significant predictor of reduced cognitive function 25 years later. In this cohort, 57.7% had never received antihypertensive medication.; another report dealing with inhabitants aged 65 to 102 years at baseline in East Boston did not show a linear association of BP with cognitive decline. The only suggestive finding was that an SBP of 160 mmHg or higher 9 years before was associated with a 14% increase in the error rate on the mental status questionnaire, relative to the reference SBP of 130 to 139 mmHg (10). The baseline SBP and diastolic BP (DBP) had a U-shaped association with errors. The problem of measuring BP is an important methodological issue in studies of the relationship between BP and cognition. Previous epidemiological studies of hypertension were based on casual measurements of BP. Currently, noninvasive ambulatory BP monitoring (ABPM) has

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been able to be used to study BP under normal living conditions. There is some evidence that ABPM is superior to office BP measurement in predicting hypertension and related target organ damage (11, 12). Shimada et al. (12) demonstrated that 'non-dipping' in older individuals was associated with white-matter damage, and concluded that the presence of a nocturnal fall in older hypertensives could prevent hypertensive vascular damage. On the other hand, a study by Kario et al. (13) suggested that extreme nocturnal dipping may be an additional risk factor for stroke and that there may be a J-shaped relationship between dipping status and organ damage. These results suggested that a nocturnal BP fall is more important than a single casual BP measurement when considering cognitive impairment.

However, there are few studies on the correlation between the fall in nocturnal BP and cognitive function. Therefore, we evaluated the possibility that the nocturnal fall in BP is associated with reduced cognitive function in both antihypertensive drug users and non-users. We examined BP using ABPM to reduce any measurement bias resulting from the use of limited numbers of BP readings.

Methods

Subjects:

The study was a cross-sectional survey of elderly subjects aged 60–93 years living in the community. The study was conducted between November 1998 and July 2000 in three towns, in Ibaraki Prefecture in Japan. We recruited participants for this study by visiting health education classes for senior clubs consisting of 30 to 50 members. Each town has 20 to 30 clubs, and a third to half of the members of each club attended the health education classes, suggesting that subjects with differing levels of health awareness were also included. Only those who agreed to the study and gave informed consent were enrolled as participants. A total of 266 elderly people participated. A face-to-face interview based on a questionnaire and ABPM were conducted at the subject's home. In addition, the subjects were screened at the interview for past and present cerebrovascular episodes, heart disease, diabetes mellitus, hypercholesterolemia, and for a history of using medications such as antihypertensive drugs and benzodiazepine drugs by asking them to show all their prescribed drugs. We confirmed this information by examining the written information given to the patients by their community pharmacy or hospital pharmacy. Exclusion criteria were applied to subjects who had a history of cerebrovascular episodes (including TIA) or who suffered severely impaired cognition as assessed by the quality of their answers to questions on their birthday and age in the Mental State Questionnaire (MSQ) (14) or who complained of disturbed sleep. Individuals with coronary heart disease, diabetes mellitus, or other major complications and individuals with or without antihypertensive treatment remained eligible unless they met the exclusion criteria. Of these participants, 60 who had a history of cerebrovascular episodes including TIA and two participants who could not complete the ABPM were excluded from the analysis. No one complained of disturbed sleep in their diary records. We included the benzodiazepine

users because this drug is commonly used among the elderly in Japan, and Hanlon et al. (15) reported that current benzodiazepine use is associated with impaired memory among community-dwelling elderly subjects. Finally, 204 of the participants were eligible for the study.

Casual BP and 24-hour BP monitoring:

Casual BP was measured at the subject's home in the sitting position by an investigator with a semi-automatic BP measuring device (HEM-722C, Omron Life Science Co. Ltd., Tokyo, Japan) using the cuff-oscillometric method. The average of four BP readings measured on two consecutive days was defined as the casual BP.

Noninvasive ABPM was carried out for 24 hours with an automatic ABP monitor (A&D TM 2421, A&D Co. Ltd., Tokyo, Japan) (16) on a weekday (Monday to Friday) for the sake of this study. However, each subject's results were returned to his or her physician. The device was preset to measure BP every 30 minutes during the day (6:00–22:00) defined as daytime and every 60 minutes during the night (22:00–6:00) defined as nighttime. Ambulatory data were obtained by the oscillometric method. Daytime BP and nighttime BP were calculated as the mean BP during the daytime and the nighttime. The subjects were asked to carry out their normal activities during the monitoring period, with the only exception being to hold their arms still at the time of each BP reading, and to keep a diary in which they reported their activities. Participants with disturbed sleep were not included in the study.

The nocturnal fall in DBP was calculated as (daytime DBP–nighttime DBP)/daytime DBP and expressed as a percentage. Based on the nocturnal fall in BP, we classified participants into two groups; non-dippers (nocturnal BP fall<10%) and dippers (nocturnal BP fall≥10%) (17). We further divided the dippers into two groups: normal dippers (nocturnal BP fall≥10%, but <20%) and extreme dippers (nocturnal BP fall≥20%). The nocturnal fall in SBP was calculated as well.

Cognitive assessment:

Cognitive function was assessed based on the MMSE (18) with scores ranging from 0 points (worst) to 30 points (best). MMSE was chosen as a test of cognitive function (18) because of its frequent use in epidemiological studies (7, 19–22), because it enables one to conveniently measure cognitive function in many subjects for a short time, and because the sensitivity of orientation items is low but the sensitivity of several non-orientation items is high (23). Cognitive impairment was defined as a score of less than 24 (19). A Japanese version of the MMSE by Mori et al. (24) was used and the sensitivity and specificity for detecting cognitive deficits (MMSE≤23) was 0.83 and 0.93, respectively (24). One of the authors who is a coordinator of long-term care insurance for community-living elderly conducted the assessment.

Medication compliance:

The rate of compliance was calculated by the pill count method, which showed what percentage of the prescribed medication a participant took (20). An investigator counted the prescribed drugs not taken and furthermore asked subjects how

often they had not taken their medications. Good compliance was defined as more than 80% adherence to the prescribed regimen of antihypertensive drugs (20).

Statistical analysis:

Differences in continuous variables between subjects with MMSE $\leq$ 23 and those with MMSE $\geq$ 24 were evaluated using an unpaired Student's t-test. Sex, current alcohol intake, current smoking, and body mass index (BMI) $\geq$ 25 (kg/m²), were scored as dichotomous variables. Categorical data were compared using the χ^2 test. Differences in continuous variables among the three levels of nocturnal fall in BP (non-dipper, normal dipper, and extreme dipper) were evaluated with a one-way ANOVA. When there were differences among the three groups, a post hoc analysis was conducted with the Bonferroni test to identify factors. In addition, a logistic regression analysis for cognitive impairment was performed by stratifying the sample into three groups according to the level of nocturnal fall in BP. The reference category was the normal dipper (a nocturnal fall of BP $\geq$ 10%, but $<$ 20%). A multiple logistic regression model was used to calculate the odds ratios for cognitive impairment, adjusting for potential confounding variables (age, sex, education, diabetes mellitus, current alcohol intake, current smoking, heart disease, and hypercholesterolemia, BMI $\geq$ 25, and benzodiazepine use), and the nocturnal falls in SBP and DBP were separately entered into the model. Data were analyzed using the SPSS 8.0 statistics package. A value of $P<0.05$ was considered significant.

Results

Overall, 204 of the subjects were eligible for the study. The mean age and education level of eligible participants were 75.2 $\pm$ 7.2 years (range 60 to 90 years) and 9.1 $\pm$ 2.4 years, respectively. Of the eligible participants, 63 (30.9%) were male and 126 (61.7%) were being treated with antihypertensive drugs. Approximately 83% of treated hypertensives had more than 80% adherence to the prescribed regimen of antihypertensive drugs, and of treated hypertensives, 85.7% were prescribed calcium channel blockers.

Of the 204 subjects, 54 (26.5%) were benzodiazepine

users. Users of Benzodiazepine with and without antihypertensive drugs numbered 41 (32.5%) and 13 (16.7%), respectively, and a significant difference was observed between them. However, the prevalence of cognitive impairment did not differ significantly between benzodiazepine users and non-users; 13 out of 54 (24.1%) and 35 out of 150 (23.3%), respectively.

Of the eligible participants, the prevalence of subjects with MMSE $\leq$ 23 and either hypercholesterolemia, or diabetes mellitus as a vascular risk factor was 16.7% (8), or 4.2% (2), respec-

Table 1 Comparison between subjects with MMSE $\geq$ 24 and those with MMSE $\leq$ 23 among antihypertensive drug users

	MMSE $\geq$ 24 (n=96)	MMSE $\leq$ 23 (n=30)
Age, yr	74.3 $\pm$ 6.9	77.6 $\pm$ 6.7*
Male	33 (34.4%)	6 (20.0%)
Education, yr	9.1 $\pm$ 2.2	8.1 $\pm$ 1.9*
Current alcohol intake	34 (35.4%)	7 (23.3%)
Current smoking	12 (12.5%)	4 (13.3%)
Benzodiazepine use	31 (32.3%)	10 (33.3%)
Heart disease	32 (33.3%)	11 (36.7%)
Diabetes mellitus	8 (8.3%)	2 (6.7%)
Hypercholesterolemia	29 (30.2%)	7 (23.3%)
BMI $\geq$ 25, kg/m ²	34 (35.4%)	12 (40.0%)
Non-compliance	16 (16.7%)	5 (16.7%)
Casual SBP/DBP, mmHg	147.6 $\pm$ 19.9/82.0 $\pm$ 10.4	144.6 $\pm$ 18.8/80.5 $\pm$ 8.1
Day SBP/DBP, mmHg	137.8 $\pm$ 14.0/81.7 $\pm$ 9.6	136.9 $\pm$ 12.7/78.4 $\pm$ 7.3
Night SBP/DBP, mmHg	123.1 $\pm$ 16.8/72.1 $\pm$ 9.4	120.8 $\pm$ 16.2/68.2 $\pm$ 9.9
Day-Night SBP, mmHg	10.7 $\pm$ 7.7	11.6 $\pm$ 9.8
Day-Night DBP, mmHg	11.5 $\pm$ 7.7	13.0 $\pm$ 9.6
SBP		
Non-Dipper	41 (42.7%)	14 (46.7%)
Normal Dipper	46 (47.9%)	12 (40.0%)
Extreme Dipper	9 (9.4%)	4 (13.3%)
DBP		
Non-Dipper	39 (40.6%)	12 (40.0%)
Normal Dipper	47 (49.0%)	11 (36.7%)
Extreme Dipper	10 (10.4%)	7 (23.3%)

Values are means $\pm$ SD, N (%).

* $P<0.05$ vs MMSE $\geq$ 24.

Non-dipper, nocturnal fall in BP of $<$ 10%.

Normal dipper, nocturnal fall in BP of $\geq$ 10%, but $<$ 20%.

Extreme dipper, nocturnal fall in BP of $\geq$ 20%.

Non-compliance, rate of compliance $<$ 80%.

Table 2 Characteristics of the elderly according to nocturnal BP fall among antihypertensive drug users

	Systolic BP			Diastolic BP		
	Non-Dipper (n=55)	Normal Dipper (n=58)	Extreme Dipper (n=13)	Non-Dipper (n=51)	Normal Dipper (n=58)	Extreme Dipper (n=17)
Age, yr	76.4 $\pm$ 6.8	73.8 $\pm$ 6.7	74.8 $\pm$ 8.6	76.3 $\pm$ 7.0	73.7 $\pm$ 6.4	76.1 $\pm$ 8.1
Male	18 (32.7%)	16 (27.6%)	5 (38.5%)	17 (33.3%)	18 (31.0%)	4 (23.5%)
Alcohol intake	19 (34.5%)	16 (27.6%)	6 (46.2%)	18 (35.3%)	17 (39.3%)	6 (35.3%)
Smoking	5 (9.1%)	9 (15.5%)	2 (15.4%)	4 (7.8%)	9 (15.5%)	3 (17.6%)
Benzodiazepine use	17 (30.9%)	20 (34.5%)	4 (30.8%)	19 (37.3%)	17 (29.3%)	5 (29.4%)
Duration of medication	12.6 $\pm$ 10.4	11.1 $\pm$ 8.8	9.4 $\pm$ 5.3	12.1 $\pm$ 9.4	12.1 $\pm$ 9.6	8.5 $\pm$ 7.0
One antihypertensive drug	31 (59.6%)	41 (65.1%)	10 (71.4%)	35 (67.3%)	33 (56.9%)	14 (73.7%)
Calcium channel blocker	23 (56.1%)	33 (61.1%)	8 (66.7%)	25 (65.8%)	26 (51.0%)	13 (72.2%)
BMI $\geq$ 25, kg/m ²	24 (43.6%)	17 (29.3%)	5 (38.5%)	16 (31.4%)	24 (41.4%)	6 (35.3%)
Education level, yr	8.7 $\pm$ 2.1	8.8 $\pm$ 2.2	9.7 $\pm$ 2.4	8.7 $\pm$ 2.1	8.8 $\pm$ 2.1	9.5 $\pm$ 2.7

Values are means $\pm$ SD, N(%).

Non-dipper, nocturnal fall in BP of $<$ 10%; normal dipper, nocturnal fall in BP of $\geq$ 10% to $<$ 20%; extreme dipper, nocturnal fall in BP of $\geq$ 20%.

tively. These rates did not differ from those of subjects without these risk factors. The prevalence of the subjects with MMSE $\geq$ 24 in the group of antihypertensive drug users and that in the group of non-users was 76.2% and 76.9%, respectively. A comparison between subjects with MMSE $\geq$ 24 and MMSE $\leq$ 23 among the antihypertensive drug users is shown in Table 1. Those with MMSE $\leq$ 23 were significantly older and had a lower education level than those with MMSE $\geq$ 24. The daytime and nighttime DBPs, but not the SBPs, of the subjects with MMSE $\leq$ 23 tended to be lower than those with MMSE $\geq$ 24,

although not by a significant amount. The prevalence of benzodiazepine use and non-compliance at less than 80% did not differ between the MMSE $\geq$ 24 subjects and the MMSE $\leq$ 23 subjects. There were no significant differences in any of the examined variables except age and education level between the MMSE $\geq$ 24 and MMSE $\leq$ 23 subjects who did not use antihypertensive drugs (data not shown).

Table 2 shows the characteristics of the three groups (non-dippers, normal dippers and extreme dippers) classified according to the magnitude of the fall in nocturnal BP among the

Table 3 Comparison of BP according to nocturnal BP fall in anti-HT (+) and in anti-HT (–) and Comparison between BP in anti-HT (+) and BP in anti-HT (–)

	Systolic BP			Diastolic BP		
	Non-Dipper (anti-HT (+) n=55) (anti-HT (–) n=28)	Normal Dipper (anti-HT (+) n=58) (anti-HT (–) n=37)	Extreme Dipper (anti-HT (+) n=13) (anti-HT (–) n=13)	Non-Dipper (anti-HT (+) n=51) (anti-HT (–) n=24)	Normal Dipper (anti-HT (+) n=58) (anti-HT (–) n=40)	Extreme Dipper (anti-HT (+) n=17) (anti-HT (–) n=14)
Casual SBP, mmHg, anti-HT(+)	146.3 $\pm$ 21.5	145.6 $\pm$ 18.0	155.1 $\pm$ 18.6	146.9 $\pm$ 22.3	145.6 $\pm$ 17.2	151.5 $\pm$ 20.0
Casual SBP, mmHg, anti-HT(–)	140.5 $\pm$ 16.5	146.0 $\pm$ 19.8	157.6 $\pm$ 20.6	141.1 $\pm$ 18.1	146.0 $\pm$ 19.8	154.1 $\pm$ 19.2
Casual DBP, mmHg, anti-HT(+)	80.3 $\pm$ 9.4	82.3 $\pm$ 10.5	83.9 $\pm$ 9.0	79.8 $\pm$ 9.4	82.7 $\pm$ 10.0	83.4 $\pm$ 10.7
Casual DBP, mmHg, anti-HT(–)	79.3 $\pm$ 11.0	81.5 $\pm$ 10.5	85.5 $\pm$ 10.0	77.5 $\pm$ 10.3	82.2 $\pm$ 10.7	85.3 $\pm$ 9.7
Day SBP, mmHg, anti-HT(+)	137.3 $\pm$ 14.3	136.5 $\pm$ 13.2	144.0 $\pm$ 12.0	135.6 $\pm$ 16.0	138.2 $\pm$ 11.1	141.8 $\pm$ 13.6
Day SBP, mmHg, anti-HT(–)	131.0 $\pm$ 14.0	135.6 $\pm$ 15.9	140.6 $\pm$ 12.3	129.7 $\pm$ 14.2	136.6 $\pm$ 15.3	138.2 $\pm$ 13.3
Day DBP, mmHg, anti-HT(+)	80.9 $\pm$ 8.9	80.3 $\pm$ 9.5	83.6 $\pm$ 9.5	78.9 $\pm$ 9.3	82.7 $\pm$ 8.9	80.8 $\pm$ 9.4
Day DBP, mmHg, anti-HT(–)	76.9 $\pm$ 9.6	79.6 $\pm$ 10.0	82.9 $\pm$ 7.3	74.8 $\pm$ 9.7	80.5 $\pm$ 9.3	82.9 $\pm$ 7.9
Day pulse, anti-HT(+)	68.7 $\pm$ 8.5	71.0 $\pm$ 8.9	70.8 $\pm$ 7.7	66.6 $\pm$ 8.1*	71.9 $\pm$ 7.9	74.0 $\pm$ 8.9
Day pulse, anti-HT(–)	72.4 $\pm$ 10.9	69.6 $\pm$ 9.6	71.1 $\pm$ 7.8	71.7 $\pm$ 11.7	70.0 $\pm$ 9.4	71.7 $\pm$ 7.7
Night SBP, mmHg, anti-HT(+)	132.3 $\pm$ 16.7*	117.0 $\pm$ 11.6	106.2 $\pm$ 10.8*	129.7 $\pm$ 19.6*	120.5 $\pm$ 10.9	108.4 $\pm$ 12.1*
Night SBP, mmHg, anti-HT(–)	125.8 $\pm$ 13.7*	115.7 $\pm$ 14.2	107.4 $\pm$ 11.1	123.7 $\pm$ 14.9	118.1 $\pm$ 14.4	107.7 $\pm$ 11.7
Night DBP, mmHg, anti-HT(+)	76.1 $\pm$ 8.9*	68.3 $\pm$ 8.3	63.6 $\pm$ 9.2	75.6 $\pm$ 9.3*	70.4 $\pm$ 7.9	60.7 $\pm$ 7.8*
Night DBP, mmHg, anti-HT(–)	72.4 $\pm$ 8.7	67.4 $\pm$ 9.8	64.2 $\pm$ 7.7	75.6 $\pm$ 10.0	68.4 $\pm$ 8.7	62.7 $\pm$ 7.6
Night pulse, anti-HT(+)	58.9 $\pm$ 8.5	60.3 $\pm$ 7.7	57.7 $\pm$ 7.9	56.8 $\pm$ 7.6*	61.0 $\pm$ 7.9	62.0 $\pm$ 8.2
Night pulse, anti-HT(–)	63.3 $\pm$ 12.2	59.9 $\pm$ 9.7	58.7 $\pm$ 7.7	62.8 $\pm$ 13.7	59.6 $\pm$ 8.3	61.4 $\pm$ 9.9
24-hr SBP, mmHg, anti-HT(+)	136.3 $\pm$ 14.6	132.7 $\pm$ 12.8	136.3 $\pm$ 11.0	134.5 $\pm$ 16.5	134.7 $\pm$ 10.7	135.0 $\pm$ 12.5
24-hr SBP, mmHg, anti-HT(–)	130.0 $\pm$ 13.8	131.7 $\pm$ 15.5	134.0 $\pm$ 12.0	128.5 $\pm$ 14.1	133.0 $\pm$ 14.9	132.2 $\pm$ 12.7
24-hr DBP, mmHg, anti-HT(+)	80.0 $\pm$ 8.6	78.0 $\pm$ 9.1	79.6 $\pm$ 8.9	78.3 $\pm$ 9.1	80.3 $\pm$ 8.6	76.8 $\pm$ 8.7
24-hr DBP, mmHg, anti-HT(–)	76.0 $\pm$ 9.2	77.2 $\pm$ 10.0	79.8 $\pm$ 7.4	74.3 $\pm$ 9.7	78.1 $\pm$ 9.2	79.4 $\pm$ 7.9
24-hr pulse, anti-HT(+)	67.0 $\pm$ 8.6	69.1 $\pm$ 8.4	68.2 $\pm$ 7.5	64.9 $\pm$ 8.3*	69.8 $\pm$ 7.6	71.6 $\pm$ 8.6
24-hr pulse, anti-HT(–)	70.6 $\pm$ 11.0	67.7 $\pm$ 9.3	68.7 $\pm$ 7.5	70.0 $\pm$ 11.9	68.0 $\pm$ 8.9	69.7 $\pm$ 7.9

Values are means $\pm$ SD, N (%); * P<0.05 vs normal dipper, anti-HT (+), user of antihypertensive drugs; anti-HT (–), non-user of antihypertensive drug. Non-dipper, nocturnal fall in BP of <10%; normal dipper, nocturnal fall in BP of $\geq$ 10% to <20%; extreme dipper, nocturnal fall in BP of $\geq$ 20%.

antihypertensive drug users. There were no significant differences among the three groups in terms of demographic characteristics including current benzodiazepine use, duration of antihypertensive drug use, or the class and number of antihypertensive drugs administered (Table 2). Among the antihypertensive drug users, no significant differences were found between the three groups in casual BP or daytime BP (Table 3). However, the nighttime BPs were significantly higher in the non-dippers than normal dippers, and significantly lower in the extreme dippers than normal dippers (calculated from SBP or DBP). Among those not using antihypertensive drugs, although nighttime SBP was significantly higher in the non-dippers than

normal dippers (calculated from SBP), there were no significant differences among the three groups (calculated from SBP or DBP) in casual BP, daytime BP or nighttime BP. There were no significant differences in casual BP, daytime BP or nighttime BP between the antihypertensive drug users and the non-users in all three groups: non-dippers, normal dippers, and extreme-dippers (calculated from SBP or DBP) (Table 3).

Fig. 1 shows the prevalence of the subjects with MMSE $\leq$ 23 in the three groups among subjects who either use or do not use antihypertensive drugs. Among the users, a J-shaped relationship between dipping status and cognitive impairment seems apparent, however, it is not significant by χ^2 test. In contrast, a

Table 4 Odds ratio of cognitive impairment for elderly with normal dippers, non-dippers, and extreme dippers determined by logistic regression analysis

	No	Odds Ratio (95% CI)	Odds Ratio (95%CI) [†]	Odds Ratio (95% CI) [‡]
<Antihypertensive Drug Use>				
Systolic BP	126			
Normal Dipper	58 (46.0%)	1	1	1
Non-Dipper	55 (43.7%)	1.31 (0.54–3.15)	1.21 (0.48–3.07)	1.37 (0.49–3.88)
Extreme Dipper	13 (10.3%)	1.70 (0.45–6.49)	2.27 (0.53–9.66)	2.97 (0.64–13.85)
Diastolic BP	126			
Normal Dipper	58 (46.0%)	1	1	1
Non-Dipper	51 (40.5%)	1.31 (0.52–3.30)	1.17 (0.45–3.06)	1.30 (0.45–3.75)
Extreme Dipper	17 (13.5%)	3.00 (0.93–9.62)	3.21 (0.89–11.53)	4.18 (1.07–16.41)*
<No Antihypertensive Drug Use>				
Systolic BP	78			
Normal Dipper	37 (47.4%)	1	1	1
Non-Dipper	28 (35.9%)	2.03 (0.65–6.36)	1.33 (0.33–5.30)	1.30 (0.28–6.12)
Extreme Dipper	13 (16.7%)	0.78 (0.14–4.34)	1.18 (0.18–7.55)	0.91 (0.10–7.90)
Diastolic BP	78			
Normal Dipper	40 (51.3%)	1	1	1
Non-Dipper	24 (30.8%)	1.00 (0.31–3.22)	0.94 (0.22–3.97)	0.79 (0.16–4.04)
Extreme Dipper	14 (17.9%)	0.50 (0.10–2.63)	1.19 (0.19–7.53)	1.17 (0.13–10.71)

CI, confidential interval.

[†], adjusted by age, sex, education level.

[‡], adjusted by age, sex, education level, diabetes mellitus, heart disease, hypercholesterolemia, current alcohol intake, Current smoking, benzodiazepine use, BMI $\geq$ 25.

Non-dipper, nocturnal fall in BP of <10%; normal dipper, nocturnal fall in BP of $\geq$ 10% to <20%; extreme dipper, nocturnal fall in BP of $\geq$ 20%.

* P<0.05 vs normal dipper, Hosmer and Lemeshow Goodness-of-Fit Test, 0.43.

Fig. 1 Prevalence of subjects with MMSE $\leq$ 23 in 3 nocturnal BP fall groups among with and without antihypertensive drug users. Anti-HT: antihypertensive, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table 5 Odds ratio of cognitive impairment for the elderly with nighttime BP in reference to the 10th to 90th percentile by multiple logistic regression analysis

	No	Nighttime BP (mean±SD), mmHg	Odds Ratio (95%CI) [†]
<Antihypertensive Drug Use>			
Night SBP			
SBP<10th percentile	9	96.3±3.1	3.19 (0.61–16.7.)
10th≤SBP<90th percentile	104	120.7±10.4	1
SBP≥90th percentile	13	154.6±16.5	0.4 (0.07–2.42)
Night DBP			
DBP<10th percentile	9	54.1±3.1	4.86 (0.90–23.77)
10th≤DBP<90th percentile	102	70.3±6.8	1
DBP≥90th percentile	15	87.5±3.9	0.32 (0.04–2.93)
<No Antihypertensive Drug Use>			
Night SBP			
SBP<10th percentile	11	96.8±4.5	0.47 (0.04–5.53)
10th≤SBP<90th percentile	60	118.5±10.2	1
SBP≥90th percentile	7	146.7±4.6	1.99 (0.27–14.76)
Night DBP			
DBP<10th percentile	12	54.0±2.5	0.41 (0.04–4.20)
10th≤DBP<90th percentile	60	69.8±6.2	1
DBP≥90th percentile	6	86.3±3.0	0.92 (0.05–16.16)

CI, confidential interval; SBP, systolic blood pressure; DBP, diastolic blood pressure.

†, adjusted by age, sex, education level, diabetes mellitus, heart disease, hypercholesterolemia, current alcohol intake, Current smoking, benzodiazepine use, BMI≥25.

linear relationship between dipping status and cognitive impairment is seen among the non-users although it is not significant.

Table 4 shows the odds ratios for cognitive impairment (MMSE≤23) derived using logistic regression analysis. By multiple logistic regression analysis, the extreme dippers (calculated from DBP not SBP) in the group of antihypertensive drug users were more associated with cognitive impairment than the normal dippers; the odds ratio (95% CI; Confidential Interval) adjusted for age, sex, education level, and other possible confounding variables amounted to 4.18 (95% CI: 1.07–16.41). We did not observe this association in the subjects who were not using antihypertensive drugs.

We tried to evaluate the association between cognitive impairment and nighttime mean BP (SBP or DBP). However, after adjusting for possible confounding factors (age, sex, education level, diabetes mellitus, heart disease, hypercholesterolemia, alcohol intake, smoking, benzodiazepine use, BMI≥25), we could not find a significant linear association between them by multiple logistic regression analysis in antihypertensive drug users and non-users (data not shown). Then, we divided the participants into 3 groups; nighttime BP (SBP or DBP) at the 10th percentile, 10th to 90th percentile, and 90th percentile (mean BP is shown in Table 5). We examined the relationship between nighttime BP at the 10th percentile and cognitive impairment by multiple logistic regression analysis in reference to elderly subjects with a nighttime BP at the 10th to 90th percentile. The odds ratio for cognitive impairment adjusted by possible confounding factors in the elderly with a nighttime DBP at the 10th percentile in antihypertensive drug users was 4.86 (95% CI, 0.90–23.77) (Table 5). No significant relationship was seen between cognitive impairment and nighttime DBP at the 10th percentile. In addition, no significant association was found between cognitive impairment and nighttime SBP in the antihypertensive drug user group. Furthermore,

there was no significant relationship between cognitive impairment and nighttime BP calculated from SBP or DBP in the non-users (Table 5). We could not find a significant relationship between nighttime BP and cognitive impairment.

Discussion

In this community-based population of elderly people, we examined the relationship between the fall in nocturnal BP and cognitive function as assessed using the MMSE. One new finding in the present study is that the elderly subjects with a marked nocturnal BP fall (≥20% of the daytime DBP) showed more cognitive impairment than those with a normal nocturnal BP fall (10% to 20% of the daytime DBP) in the antihypertensive drug users group only.

Some studies (21, 22) have reported that antihypertensive treatment is effective in preventing cognitive impairment. The Syst-Eur trial (21) recruited older (≥60 years) participants with isolated systolic hypertension (ISH) taking nitredipine during a 2-year follow-up, and showed that active antihypertensive treatment reduced the incidence of dementia by 50%, while the Kungsholmen Project (22) recruited community-dwelling elderly aged 75 and older, followed them up for 3 years, and showed that the subjects receiving diuretic monotherapy had an adjusted relative risk for dementia of 0.6 (95% CI, 0.4–0.9) compared with untreated patients. In contrast to the results from these active antihypertensive treatment studies, some studies (25–27) have suggested that organ damage may result from over treatment of hypertension in the elderly. Guo et al. (26) found in subjects aged 75–101 that in the antihypertensive drug users, those with a low DBP were more likely to have dementia. In a subanalysis of the Systolic Hypertension in the Elderly Program (SHEP) (25) among recruited participants with ISH, a decrease of 5 mmHg in DBP increased the risk for cerebrovas-

cular events in the active hypertension treatment group only, not in the placebo group. In the Rotterdam Study (28), a J-shaped relation between DBP and the incidence of stroke existed in treated hypertensive subjects even though subjects with ISH were excluded.

In many studies, as the association of BP and cognitive impairment was investigated on the basis of a single office BP measurement, aggressive antihypertensive therapy in ISH treatment that reduces occasional high daytime BP may have triggered the nighttime onset of silent cerebral infarction and ischemic stroke by exacerbating nocturnal hypotension (27). We thought that evaluating the nocturnal BP fall by ABPM is important. Although the 24-hr average BP is more reproducible than the office BP (29), the reproducibility of the circadian variability or day-night differences in BP assessed by ABPM may not be satisfactory (30, 31). Repeated performance of the 24-hr ABPM over 7 days has been addressed (32), however, it faces practical problems. As ambulatory physical activity has been reported to influence the reproducibility of BP variation (32), we asked the participants to do their usual activities as much as possible while measuring 24-hr ABPM.

There has been little research on the association between the fall of nocturnal BP and cognitive impairment. Boxel et al. (33) tried to examine an association between nondipping and cognitive performance in community residents aged 28–82 years and reported that a reduced drop in nocturnal BP was associated with memory deficits. Kario et al. (13) reported that extreme dippers ($\geq 20\%$ of awake SBP) showed more advanced silent cerebrovascular damage than patients with a moderate nocturnal fall in BP (10% to 20% of awake SBP) using MRI techniques. We assumed that, as some of the dippers (extreme dippers) were positively related to cognitive impairment, and others (normal dippers) were negatively related to cognitive impairment according to the degree of nocturnal BP fall, cognitive impairment may not be linearly correlated with nocturnal BP fall. From this point of view, we divided the dippers into two subgroups: normal dippers and extreme dippers. As shown in Fig. 1, the prevalence of the subjects with MMSE ≤ 23 was different in the three groups with and without antihypertensive drug users. Our data suggested that the extreme dip in DBP in the antihypertensive drug users group was associated with cognitive function.

From our result, no association was found between cognitive impairment and nighttime BP. Our result suggests that nocturnal BP fall is more important than nighttime BP when examining cognitive impairment. We found that an extreme nocturnal BP fall in DBP as assessed by ABPM was associated with cognitive impairment in antihypertensive drug users. The mechanism of cerebral autoregulation which maintains a stable state of cerebral blood flow under varying BP seems to be

different between hypertensive elderly and normotensive elderly, and both the upper and lower limits of autoregulation are shifted to higher levels in hypertensive subjects (34). Hypertensive elderly patients with atherosclerotic cerebral lesions are thought to be more susceptible to cerebral ischemia when their BP drops. That may be the reason why the risk of cognitive impairment in extreme-dippers among antihypertensive drug users is greater than that for non-users.

From our results, antihypertensive therapy leading to an optimal BP level is effective at preventing dementia. On the other hand, it is possible that an excessive reduction of nocturnal diastolic BP caused by antihypertensive drugs may lead to unrecognized silent cerebral infarctions that may induce cognitive impairment. As decreased cerebral blood flow is known to occur in both Alzheimer's disease and vascular dementia, and the degree of reduction generally correlates with the severity of dementia (35, 36), it seems possible that a low BP might accelerate the process of dementia by lowering cerebral blood flow.

One-sixth of stroke patients have preexisting dementia (37), and cognitive impairment may be a manifestation of clinically unrecognized stroke (38). We had better consider the nocturnal BP fall by ABPM in antihypertensive drug users.

We recognize the limitations of this study: i.e. that it is a cross-sectional survey, a small number of subjects were used and only one measurement of 24-h ABPM was made. In addition, there may be other factors that influence cognitive function, although we excluded subjects with a history of cerebrovascular episodes (including TIA) and those with severely impaired cognition. One of the factors that influence cognitive function is current benzodiazepine use, which was reported to be associated with a poorer memory among community-living elderly. However, we could not find this association in the present study.

In conclusion, we found that the extreme dippers suffered cognitive impairment 4.18 times more than the normal dippers among antihypertensive drug users only. Although casual BPs and daytime BPs in the extreme dippers were not different from those in the normal dippers, nighttime BPs were significantly lower in our study. It seems important to consider the reduction in nocturnal BP by monitoring ABP when conducting antihypertensive drug treatment. Prospective studies are needed to identify whether or not an excessive fall in nocturnal BP is a risk for cognitive impairment in antihypertensive drug users.

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