ORIGINAL ARTICLE

Blood Pressure and Heart Rate Variability in Alzheimer's Disease

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Background and Purpose   Altered blood pressure (BP) and heart rate variations (HRVs) have been reported in Alzheimer's disease (AD). However, it is unclear how these two manifestations are associated with AD. Therefore, the objective of this study was to investigate BP and heart rate variability in AD compared to that in normal controls, patients with subjective memory impairment (SMI), and patients with mild cognitive impairment (MCI).

Methods   Case-control comparisons were made among AD (n=37), MCI (n=24), SMI (n=17), and controls (n=25). All patients underwent clinical and neuropsychological assessments with 24-h ambulatory BP and Holter monitoring.

Results   Patients with AD had higher pulse pressures than those in other groups. In addition, AD patients experienced blunted nocturnal BP dipping associated with declining cognitive status. AD patients also had larger ranges of HRV in parasympathetic domains compared to other groups, especially at night.

Conclusions   Our results suggest that diurnal sympathetic and parasympathetic cardiac variability were significantly disturbed in mild cholinesterase-naïve AD patients. This may be an indirect sign of disturbed integrity to the sleep-wake cycle in mild AD.

Key Words   Alzheimer's disease, blood pressure, heart rate, sympathetic, parasympathetic, variation.

INTRODUCTION

Alzheimer's disease (AD) can damage several central nervous structures associated with autonomic dysfunction, including hypothalamus, locus ceruleus, limbic system, insular cortex, and the lower brainstem.[1-4] AD patients also exhibit various circadian autonomic patterns, including circadian body temperature dysfunction,[5,6] sleep-wake alternation,[7] and disturbed day-night blood pressure (BP) dipping.[8] However, autonomic involvement in AD is still poorly understood. Chronobiological changes with distinct parasympathetic impairment and increased sympathetic function have been reported in AD.[9-11] However, other studies have found no change in the short-term and long-term circadian BP or heart rate variability in AD.[12,13]

Clinical stages preceding AD have been identified. Epidemiological studies have proposed that cohorts at risk for developing AD is comprised of older individuals with mild cognitive impairment (MCI) characterized by cognitive decline intermediate between normal aging and dementia.[14,15] In addition, recent studies have further proposed that subjects with memory impairment and normal cognitive performance [subjective memory impairment (SMI)] are an at-risk of developing AD.[16-18] The model tested in this study is based on the hypothesis that autonomic dysfunction in Alzheimer's pathology will become worse in the cascade of Alzheimer's spectrum. The parasympathetic and sympathetic functions of heart can be characterized by evaluating time-domain heart rate variability and BP variability. In this study, we determined wheth-

er heart rate and BP variability were associated with AD. We compared heart rate and BP variability among AD patients, normal controls, patients with SMI, and those with MCI.

METHODS

Subjects

This study was approved by the ethics committee of Seoul St. Mary's Hospital. Each patient gave written informed consent before participating. Patients with newly diagnosed AD from the Department of Neurology of Seoul St. Mary's Hospital were enrolled in this study. They were recruited using clinical diagnostic criteria for MCI and AD as well as comprehensive neuropsychological tests addressing five cognitive domains including attention, memory, language, visuospatial function, and frontal/executive function.[19-22] SMI was diagnosed when there was complaint of memory decline although there was no objective neuropsychological explanation in neuropsychological tests.[23,24] A total of 25 healthy elderly subjects without any neurological or psychiatric history were included as controls. Patient data such as age, sex, education status, disease duration, history of hypertension, diabetes mellitus, or dyslipidemia, and smoking status were collected. Laboratory tests that may reflect cognitive function were performed, including homocysteine, vitamin B_{12}, and folate. Patients' thyroid, hepatic, and renal functions were also assessed. Patients with any laboratory abnormalities were excluded from the study. Those with atrial fibrillation, atrial flutter, frequent ectopies, and those who were on permanent pacemakers were also excluded. General cognitive status and dementia severity were evaluated using the Korean version of Mini-Mental Status Examination. BP and heart rate monitoring were performed simultaneously after discontinuing any antihypertensive medications for 7 days. During the period, no serious clinical problem was observed.

Heart rate variability analysis

In all subjects, 24-h Holter monitoring was conducted using an Aria recorder. The recordings were subsequently analyzed using Impresario Solo system (Delmar Reynolds, Hertford, UK). While being monitored, participants lived their normal lives and recorded their activities in diaries. They also provided information on hours of rest at night. Time domain analyses of heart rate variation (HRV) were also conducted for all participants.

The time domain HRV analysis was derived from a direct measurement of normal-to-normal R-R over a 24-hour period, including day time (from 8 am to 9 pm) and night time (from 11 pm to 6 am). The following time domain HRV parameters were calculated: mean of all normal RR intervals (mRR), standard deviation of N-N intervals (SDNN), mean of 5 min standard deviation of NN interval durations (SDNN index), root mean square successive NN deltas (RMS-SD), percent of difference between adjacent normal RR intervals greater than 50 ms (pNN50) and standard deviation of 5 min means of NN intervals (SDANN).[25] The first three parameters were used to reflect sympathetic and parasympathetic functions. The next two parameters were used because they were associated with parasympathetic function. The last parameter was used because it was related to sympathetic function alone.[25]

Blood pressure variability analysis

Automated 24-hour BP recording instruments (Mobil-O-Graph NG, I.E.M., Stolberg, Germany) were used to measure BP every 15 min during the daytime and every 30 min at night. The following parameters were evaluated: average systolic and diastolic BP and heart rate for the day time, night time, and 24-h periods. Any nocturnal falls in BP and heart rate were calculated as percent changes with daytime and nighttime mean values. Subjects with less than 10% nocturnal fall in mean BP were considered "non-dippers" and those with pathological increase in nocturnal BP were categorized as "reverse dippers".[26,27] Nocturnal hypertension was defined according to the 2007 European Hypertension Society/European Cardiology Society guidelines (i.e., average nighttime BP ≥120/70 mm Hg).[28,29] BP variability was calculated as within-subject standard deviation of mean systolic blood pressure during the day time and night time.[30-32]

Data analysis

One-way analysis of variance or analysis of covariance (with Bonferroni post-hoc testing) were used to compare means among groups. Pearson's χ^2 tests were used to compare the frequencies of categorical variables. Statistical software SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses. Statistical significance was considered when p value was less than 0.05.

RESULTS

Of the 103 subjects (28 males and 75 females; mean age ±SD: 69.9±8.9 years; mean education duration: 11.4±5.4 years), 25 were normal controls, 17 had SMI, 24 had MCI, and 37 had AD. These groups had similar baselines of sex distribution, symptom duration, education, hypertension, diabetes mellitus, and cigarette smoking (Table 1). The mean age of AD patients was higher than that of the controls and subjects with SMI. However, AD patients had lower Mini-Mental State Ex-

amination scores than SMI patients, MCI patients, and controls (Table 1).

AD patients also had higher pulse pressures than the controls. Nocturnal BP dipping in patients seemed to be reversely associated with decreasing cognitive status in the order of AD, MCI, SMI, and normal controls (Table 2). The frequency of non-dippers was not significantly different among groups. However, nocturnal BP reverse dippers were more prevalent

in the AD group than those in other groups. There was no significant difference in daytime and nighttime BP variations among groups. However, the AD group had greater variations in RMS-SD, SD of successive NN delta, and pNN50 domains compared to those in the other groups, especially at night. These variations reflected parasympathetic dysfunction during nighttime and at asleep (Table 3).

Table 1. Demographics and clinical characteristics of subjects

	Controls (n=25)	SMI (n=17)	MCI (n=24)	AD (n=37)	p-value	Post hoc test
Age, years, mean±SD*	67.4±4.8	64.1±9.2	69.5±8.0	74.7±9.1	<0.001	AD>controls=SMI, MCI=AD, controls=SMC=MCI
Sex, male (%)‡	6 (24.0)	6 (35.3)	9 (37.5)	7 (18.9)	0.353	
Education, years, mean±SD*	12.8±3.6	10.9±5.7	12.2±4.2	10.2±6.7	0.226	
Disease duration, years, mean±SD*	-	1.2±0.9	1.7±2.2	3.1±4.8	0.180	
Hypertension (%)‡	4 (16.0)	5 (29.4)	9 (39.1)	16 (43.2)	0.140	
Diabetes mellitus (%)‡	3 (12.0)	4 (25.3)	4 (17.4)	8 (21.6)	0.744	
Current or ex-smoker (%)‡	7 (28.0)	3 (17.6)	3 (12.5)	3 (8.1)	0.192	
MMSE†	29.1±1.7	27.1±3.6	26.7±2.2	20.1±5.1	<0.001	AD<controls=SMI=MCI

Values were presented as means (and standard deviations) or raw numbers of patients (percentage).
*Analyses were performed using one-way analysis of variance, †Analysis of covariance, and ‡Chi-square test.
AD: Alzheimer's disease, MCI: mild cognitive impairment, MMSE: Mini-Mental State Examination, SMI: subjective memory impairment.

Table 2. Blood pressure variability

	Controls (n=25)	SMI (n=17)	MCI (n=24)	AD (n=37)	p-value
Daytime					
SBP	115.2±9.1	120.1±16.3	115.0±11.8	119.8±15.8	0.371
DBP	71.4±7.8	74.8±8.9	69.1±7.7	69.1±8.8	0.095
Pulse	71.8±16.0	76.2±7.4	71.1±7.4	69.2±9.8	0.196
Pulse pressure	43.9±7.4	45.4±10.2	45.9±9.4	50.8±11.2	0.037†
Nighttime					
SBP	107.1±11.6	113.7±13.9	110.7±10.9	116.4±18.9	0.106
DBP	65.7±8.9	69.7±8.1	67.0±8.5	67.7±10.8	0.605
Pulse	65.2±8.8	66.9±9.8	63.4±6.7	62.0±9.6	0.241
Pulse pressure	41.3±7.7	43.9±8.8	43.7±8.7	48.6±12.3	0.035†
Dipping	7.5±6.7	5.8±8.7	3.2±6.8	2.5±7.3	0.041†
Non-dipper (%)*	19 (76.0)	11 (64.7)	20 (83.3)	29 (78.4)	0.567
Reverse dipper (%)*	2 (8.0)	4 (23.5)	7 (30.4)	13 (36.1)	0.092
Nocturnal hypertension (%)*	3 (12.0)	5 (29.4)	7 (29.2)	15 (40.5)	0.117
Morning surge, SBP	115.8±14.6	119.5±18.2	117.4±12.5	124.5±20.9	0.300
Daytime					
SD SBP	12.0±4.8	13.4±4.1	12.6±3.9	13.2±4.0	0.637
SD DBP	7.8±3.1	9.8±3.6	9.0±2.9	8.9±2.6	0.171
SD pulse	8.1±2.0	8.6±2.4	8.5±2.7	8.6±3.5	0.894
Nighttime					
SD SBP	10.0±3.1	13.0±6.2	10.8±2.8	10.1±5.1	0.132
SD DBP	8.3±2.8	9.1±4.2	8.6±2.7	7.6±3.6	0.424
SD pulse	6.2±2.7	5.8±2.5	6.4±2.2	4.9±2.8	0.091

Values were presented as means and standard deviations or raw numbers of patients (percentage).
Analyses were performed using analysis of covariance test and *Chi-square test, †p<0.05.
AD: Alzheimer's disease, DBP: diastolic blood pressure, MCI: mild cognitive impairment, SBP: systolic blood pressure, SD: standard deviation, SMI: subjective memory impairment.

DISCUSSION

In line with the Braak schema for pathogenetic sequences in AD, two main brain structures (insular cortex and brain-

stem) can be involved progressively in autonomic controls.[33] A deficit in central cholinergic function could likely lead to autonomic dysfunction.[34] These structures might be affected by neurodegeneration in a "preclinical stage". The autonomic

Table 3. Heart rate variability

	Controls (n=25)	SMI (n=17)	MCI (n=24)	AD (n=37)	p-value
HRV of all qualified beats (SDNN)					
Total record	120.9±24.9	119.4±34.0	117.7±23.8	129.2±47.8	0.605
Day	88.3±45.3	98.6±42.4	91.6±28.1	109.5±94.2	0.219
Night	119.0±33.1	106.1±31.2	115.5±31.8	117.2±48.4	0.736
D/N delta	34.4±40.7	7.5±49.5	23.8±29.9	12.8±39.0	0.098
RMS of successive NN deltas (RMS-SD), msec					
Total record	32.1±18.3	30.7±14.5	29.1±12.2	52.6±54.7	0.030*
Day	27.3±12.8	26.4±8.4	26.8±11.5	45.9±56.3	0.081
Night	34.8±26.9	31.0±15.8	30.6±14.4	55.1±53.4	0.026*
D/N delta	7.5±24.2	4.6±16.2	3.8±8.9	8.9±30.7	0.837
SD of successive NN delta (SDSD), msec					
Total record	25.0±17.5	24.1±14.1	22.1±10.9	40.6±39.3	0.024*
Day	22.4±13.7	19.7±6.7	20.1±10.3	35.0±39.5	0.066
Night	26.3±22.5	24.4±15.4	23.3±12.6	41.6±39.0	0.033*
D/N delta	5.3±19.6	4.6±14.8	3.3±7.4	6.6±23.4	0.921
Triangular index (HRV index)	18.1±3.8	16.3±4.8	16.8±3.9	17.6±6.5	0.643
Triangular interpolation (TINN), msec	534.4±137.7	516.5±166.2	526.1±131.1	547.7±183.4	0.910
Mean RR, msec					
Total record	824.4±80.7	814.2±94.0	864.2±84.4	821.8±236.7	0.050
Day	760.8±181.0	823.7±120.8	845.1±82.0	821.9±236.7	0.391
Night	844.7±82.8	826.1±147.7	892.8±111.0	915.1±153.7	0.056
D/N delta	83.9±153.1	2.3±116.4	47.7±83.1	93.3±205.4	0.217
pNN50, %					
Total record	4.6±3.7	5.2±4.9	4.2±4.7	11.5±16.4	0.019*
Day	2.9±2.5	4.5±5.3	3.3±3.9	9.6±16.5	0.044*
Night	6.1±7.1	4.8±4.0	4.8±5.3	13.0±18.0	0.020*
D/N delta	3.2±6.4	0.3±4.5	1.5±3.5	3.4±9.9	0.428
Mean of interval HRVs (SDNN index), msec					
Total record	35.3±9.3	32.8±7.0	32.8±8.4	42.5±36.3	0.307
Day	29.8±8.7	29.7±7.0	31.6±10.2	38.5±38.8	0.449
Night	36.0±12.6	34.8±9.6	35.3±11.4	44.6±33.1	0.254
D/N delta	7.5±11.8	5.1±7.8	4.9±8.4	6.1±18.7	0.909
SD of interval rates (SDANN), bpm/msec					
Total record, bpm	10.4±2.1	10.5±2.4	9.4±2.2	9.8±3.9	0.506
Total record, msec	113.4±26.2	112.0±32.8	122.3±64.4	114.0±36.3	0.840
Day, bpm	7.2±3.1	8.4±3.4	7.3±2.2	7.9±3.5	0.550
Day, msec	75.4±39.1	90.2±42.6	82.3±26.7	91.6±39.0	0.356
Night, bpm	9.8±3.3	9.2±3.5	8.7±3.0	8.5±4.6	0.627
Night, msec	109.1±35.4	101.5±41.3	104.4±31.5	97.6±39.7	0.680
D/N delta, bpm	2.5±4.9	0.9±5.1	1.4±3.0	0.6±4.3	0.371
D/N delta, msec	33.7±44.2	13.5±42.9	22.2±31.9	8.6±39.7	0.102

Values were presented as means and standard deviations. Analyses were performed with analysis of covariance test.
*p<0.05.
AD: Alzheimer's disease, HRV: heart rate variation, MCI: mild cognitive impairment, SMI: subjective memory impairment.

dysfunction might be present before the onset of clinical symptoms of dementia. This raises the question of whether cardiovascular autonomic impairment is related in stepwise pattern to cognitive spectrum of AD.[35] In this study, we found that diurnal sympathetic and parasympathetic cardiac variability were significantly disturbed in AD patients compared to healthy controls, but not in MCI or SMI patients.

Numerous studies have reported that patients with AD have experienced fluctuations in their circadian functions, include arousal and sleep architectures, core body temperature, and hormones such as cortisol and melatonin.[5-7] This suggests that AD will not only affect cognitive function, but also endocrine-vegetative function that mediates the circadian rhythmicity.[36] However, studies on circadian BP and heart rate variability in AD have produced contradictory results. Some reports have suggested that there is a loss in circadian periodicity in most AD patients, while others have found that BP and heart rate chronological rhythmicity are not abolished in AD patients.[9-13]

In this study, AD patients experienced blunted day-night dips in their mean BP compared to that of SMI patients or controls. Although the prevalence of non-dipping was not different between the control group and patient groups, there were tendencies of higher prevalence of nocturnal hypertension and reverse dippers in the AD group than that in the control group. In addition, 24-h Holter monitoring revealed disruption or enhancement in the parasympathetic function of AD patients. If the autonomic manifestations of clinical "AD" are AD-specific, these results suggest that such autonomic manifestations are also stage-specific. They might be limited to AD's clinical stages.

In the general population, abnormal BP and heart rate variability have been associated with cardiovascular morbidity and mortality. They are also independent risk factors of target organ damage, including renal impairment and cognitive dysfunction.[30,37-39] Cardiovascular autonomic failure related to generalized cholinergic dysfunction is a potential peripheral marker of AD.[1] In AD patients, relative depression of parasympathetic activity has been reported to be associated with cognitive dysfunction.[9-11] However, increased or unchanged sympathetic functions have also been reported in AD.[11-13] Our results added more information to the debate involving the association between chronobiological BP, heart rate changes, and cognitive dysfunction in mild AD. Increased parasympathetic dysfunctions at night and flattened day-night BP dips reflecting suppressed sympathetic function may be related to sleep-arousal system disorder. Such result might be an indirect sign of disturbed integrity of the sleep-wake cycle in mild AD.

In this study, pulse pressure was significant greater in AD patients compared to that of controls. Higher pulse pressure in the elderly is a recognized marker of increased arterial stiffness, atherosclerosis, white matter change, cognitive dysfunction, and ultimately dementia.[40,41] Increased pulse pressure in the elderly resulting from increased systolic pressure and decreased diastolic pressure may be related to hypoperfusion-related ischemia and alteration in white matter integrity.

This study had several strengths. One major strength of this study was its inclusion of patients with relatively early AD who had never taken cholinesterase inhibitors. Cholinesterase inhibitors can reduce heart rate variability. They can also affect sleep and arousal.[42] Because the participants in this study were never exposed to these medications, our results were less likely to be affected by such a confounder. Therefore, we can suggest that the association occurred independently of such treatment. Another strength of this study was its enrollment of patients with a comprehensive spectrum of memory disorders, including SMI and MCI. Although clinical diagnosis has always been criticized, we minimized selection bias by only including patients who had fulfilled the clinical diagnostic criteria for each disease.[19-21,23,24]

Although this study had several strengths, it also had several limitations. First, the relationships among SMI, MCI, and AD were not well understood. Even clinical AD phenotype's relationship to AD pathology was unclear given that the vast majority of neuropathology with AD did not have evidence of dementia. In addition, up to 20% of clinically diagnosed AD cases may lack amyloid-deposition.[43,44] Second, this study enrolled relatively mild and first-visit patients. Therefore, the autonomic function test results might have been skewed. Third, the proportion of hypertension in the AD group was higher than that in the control group. Most hypertensive patients were taking anti-hypertensive medications. Therefore, these data must be carefully interpreted as anti-hypertensive medications can contribute to BP and heart rate variability. In addition, we did not assess any other mechanisms that might have played a pathophysiological role in BP and heart rate variability. Finally, the interpretation of heart rate variability as a direct quantitative marker of cardiac autonomic dysfunction is controversial. No sensitive measurement methods were determined.

In summary, our results revealed that diurnal sympathetic and parasympathetic cardiac variability were significantly disturbed in cholinesterase-naïve AD patients. Further studies are needed to clarify the difference between mild AD patients and advanced AD patients and to assess the longitudinal changes during the progress of the disease.

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