

Orthostatic Hypotension Predicts a Poor Prognosis in Elderly People with Dementia

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Abstract

Objective The purpose of the present study was to assess the prevalence of orthostatic hypotension (OH) and elucidate its associations with the demographic characteristics and the prognosis in elderly subjects with dementia who visited a hospital for elderly daycare.

Methods A total of 64 outpatients (44 females) with a mean age of 84 ± 6 years who visited a hospital for daycare were enrolled in the study. The prevalence of OH and demographic characteristics were examined. Then, the subjects were followed up for 1 year. The blood pressure was measured in the supine position and immediately, 1, 3 and 5 minutes after standing. Poor outcome measures included death, hospitalization for any reason, and admission to a nursing home or geriatric facility.

Results OH was present in 17 patients (26.6%). The presence of OH was associated with a higher supine systolic blood pressure. The increase in heart rate in the standing position was also reduced in subjects with OH compared with those without. The presence of OH was associated with faster time in the timed up-and-go test compared with those without OH. During the follow-up period, 22 patients (34.4%) had a poor prognosis, of which 8 (36.4%) had OH, which tended to be higher than those with a favorable prognosis. The event-free survival rate appeared to be lower in subjects with OH than in those without.

Conclusion OH is relatively common in frail elderly patients with dementia, and it also appears to be associated with a poor prognosis.

Key words: orthostatic hypotension, mortality, elderly, frailty

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Introduction

Blood pressure (BP) variability is known to increase in elderly people most likely as a consequence of autonomic failure due to aging or atherosclerosis (1-3). The prevalence of orthostatic hypotension (OH) increases with aging, depending on complications (4). OH is related to various age-associated syndromes, such as dizziness, fall and frailty. Among elderly patients, OH is reported to be an indicator of a general lessening of physical strength or frailty and a portent of death. OH is associated with many cardiovascular (CV) diseases (5), such as coronary heart disease (6-8), stroke (9), congestive heart failure (10) and atrial fibrilla-

tion (11), and the presence of OH has also been related to an increased risk of many non-CV-related conditions, including dementia (12, 13), falls (14) and chronic kidney disease (15). Moreover, OH has been found to be related to an increase in mortality (7, 8, 16-18), although previous results are not always consistent. There are few reports on the BP variability at the time of postural changes in elderly people with dementia. Thus, the aims of this study were to assess the prevalence of OH and elucidate its associations with the demographic characteristics and the prognosis of frail elderly patients with dementia who regularly visit a hospital for daycare.

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Materials and Methods

Study population

We enrolled 64 outpatients aged 70 years or older who visited a hospital for daycare, particularly programmed for participants with dementia, from September 2012 to February 2013. Frailty is a common clinical syndrome in older adults that carry an increased risk for poor health outcomes including fall, incident disability, hospitalization, and mortality. Of these patients, those who were able to walk without assistance and maintain a standing position for at least 5 minutes were enrolled in the study. All subjects and/or their family provided their written informed consent to participate in this study.

Blood pressure measurement

The baseline BP and heart rate (HR) were measured twice in each subject while sitting, in the supine position and standing, before lunch (at least two hours after breakfast), after at least 3 minutes of rest in the sitting position, on the right and left arms simultaneously, using a validated digital electronic device (Parama-Tech PS-501). Then BP was measured in the supine position after a few minutes of rest. After the measurements of supine BP, the BP was measured 4 times; i.e., immediately, 1, 3 and 5 minutes after standing. The definition of OH according to the international consensus is a decrease in the systolic BP (SBP) ≥ 20 mmHg and/or a decrease in the diastolic BP (DBP) ≥ 10 mmHg within 3 minutes of standing as compared with supine values (19). Delayed OH was also included in the definition of OH in this study, and delayed OH is generally defined by blood pressure changes after more than 10 minutes of standing (20); however, in the present study, delayed OH was defined by blood pressure changes after 5 minutes of standing due to the difficulties in maintaining a sustained standing position in elderly patients.

Determination of the prognosis

The prognosis was assessed from the medical records one year afterward. Study subjects were divided into the favorable prognosis and the poor prognosis groups. A poor prognosis was defined if the subjects had any of the following events: death, hospitalization for any reason, or admission to a nursing home or geriatric facility.

Assessment of physical function and activity

A trained physician evaluated the timed up-and-go (TUG) test (21) for all participants. We calculated the time required for the study patients to stand up from a standard chair, walk a distance of 3m, turn, walk back to the chair and sit down again. The TUG test was performed twice, and the best time was used for the analysis. In musculoskeletal ambulation disability symptom complex (MADS), the cut-off time is reported to be 11 seconds (22), with the object of

care prevention.

Other measurements

The carotid intima-media thickness (IMT) assessed by ultrasound was used as a surrogate marker for atherosclerosis (electronic device; Toshiba: SSA-660A, Xario, using a 7.5 MHz probe). The cognitive function was assessed using the mini-mental state examination (MMSE) score by expert neurologists or psychiatrists. The methods used for this examination have been described in detail elsewhere (3). The MMSE values range from 0 to 30. We obtained clinical information according to the medical records of the subjects.

Statistical analysis

All statistical analyses were performed with the SAS statistical software program, version 9.2 (SAS Institute, Cary, USA). Values are expressed as the mean \pm SD or as percentages. Differences between groups were analyzed by the χ^2 test for categorical data and Student's *t*-test for continuous data. Kaplan-Meier curves were used for a one-way comparison of the event-free survival rate between subjects with and without OH (while using the log-rank and Wilcoxon tests for group comparisons). A two-sided $p < 0.05$ was considered to be statistically significant in all analyses.

Results

The mean age of the study subjects was 84 ± 6 years of age. There were 44 (68.8%) women and 20 (31.3%) men. The mean MMSE score was 17/30 points. The diagnosis of dementia was as follows: Alzheimer's dementia (AD) 78.1% ($n=50/64$), vascular dementia (VaD) 15.6% ($n=10/64$), and dementia with Lewy bodies (DLB) 6.3% ($n=4/64$). Hypertension (SBP and/or DBP $\geq 140/90$ mmHg and/or the use of antihypertensive drug) was observed in 79.7% of the subjects ($n=51/64$). Thirty-five study subjects (59.4%) received antihypertensive drugs. Calcium-channel blockers were used in 70.7% of the 35 patients, followed by angiotensin II receptor blockers in 56.1%, angiotensin-converting enzyme inhibitors in 9.8%, $\alpha\beta$ -blocker in 4.9%, β -blocker in 4.9%, thiazide diuretic in 17.1%, and loop diuretic in 12.2%. Diabetes mellitus (DM) was present in 7.8% of the patients ($n=5/64$) and a history of cerebrovascular disease was found in 23.4% of the subjects ($n=15/64$).

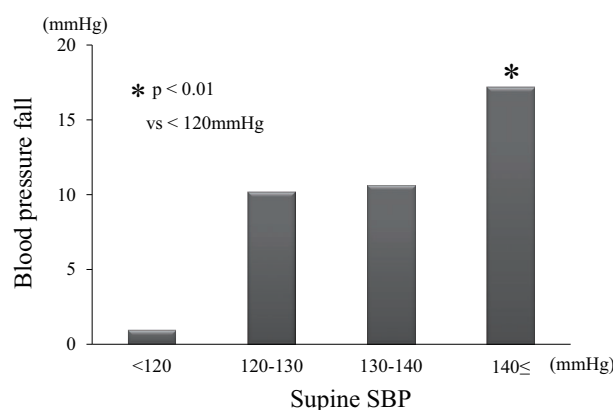
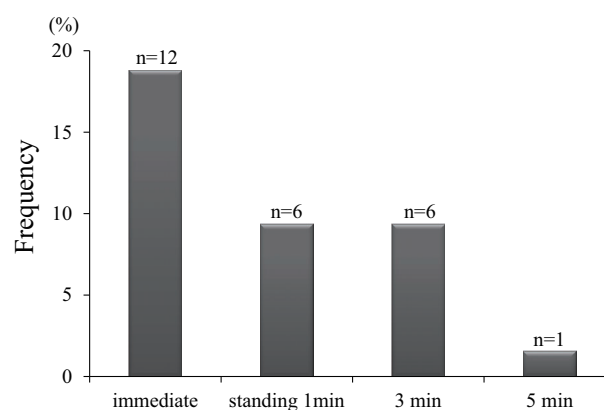
Table shows the baseline characteristics of the subjects with or without OH. OH was present in 17 subjects (26.6%). In subanalyses by dementia subtypes, OH was present in 22.0% ($n=11/50$) of AD subjects, 30.0% ($n=3/10$) of VaD subjects and 50.0% ($n=2/4$) of DLB subjects. The presence of OH was associated with a faster time on the TUG test compared with those without OH. We also found that the supine SBP was significantly higher in subjects with OH than in those without. There was no significant difference in the prevalence of OH between subjects with and without antihypertensive treatment (26.8% vs. 26.1%, $p=0.9$). The frequency of a male gender, low body mass index, thicker IMT

Table. Characteristics of Patients.

	All	Without OH (n=47)	With OH (n=17)
Gender (% male)	31.3	23.4	47.1
Age (y)	84 ± 6	84 ± 6	84 ± 8
BMI (kg/m ²)	22 ± 4	23 ± 4	21 ± 3
Supine SBP (mmHg)	131 ± 14	128 ± 12	139 ± 18*
DBP (mmHg)	75 ± 11	76 ± 12	78 ± 9
HR (beats/min)	65 ± 9	67 ± 8	63 ± 10
Immediate standing SBP (mmHg)	130 ± 18	131 ± 17	114 ± 24*
DBP (mmHg)	81 ± 14	82 ± 15	72 ± 11*
HR (beats/min)	78 ± 12	81 ± 11	74 ± 13*
Hypertension			
Antihypertensive agents (%)	59.4	63.8	64.7
diuretic (%)	18.6	17.0	23.5
MMSE score	17 ± 6	16.8 ± 6	18.2 ± 6
Diabetes mellitus (%)	7.8	6.4	11.8
eGFR (mL/min/1.73m ²)	56.6 ± 18.0	55.9 ± 17.5	58.6 ± 19.7
IMT (max)	1.2 ± 0.7	1.1 ± 0.6	1.5 ± 0.9
TUG >11sec. (%)	66.7	73.7	46.7*
Frequency of symptoms (%) (Dizziness, Loss of balance... etc)	19.0	15.2	29.4

BMI: body mass index, OH: orthostatic hypotension, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, MMSE: mini-mental state examination, IMT: intima-media thickness

* p < 0.05

**Figure 1. Relationship between decreases in the blood pressure on standing and the supine systolic blood pressure (SBP).****Figure 2. Time-dependent frequency of orthostatic hypotension after standing.**

and diuretic use tended to be higher in subjects with OH than in those without, although the difference did not reach statistical significance. There was no significant difference in the prevalence of OH between subjects with and without DM (40.0% vs. 60.0%, $p=0.5$). Even when the subjects who had DLB were excluded, the supine SBP was significantly greater in subjects with OH than in those without ($p<0.01$).

Fig. 1 shows the relationship between the magnitude of BP decrease on standing and the supine BP level. The magnitude of BP decrease on standing was significantly greater in subjects with supine SBP ≥ 140 mmHg compared with those with SBP <120 mmHg ($p<0.01$).

The frequencies of OH occurrence at each time point were 18.8% (immediate), 9.4% (standing after 1 min), 9.4% (standing after 3 min) and 1.6% (standing after 5 min) of the total subjects, respectively (Fig. 2). OH was most pronounced immediately after standing. The difference was not

influenced by the presence or absence of antihypertensive treatment (data not shown).

Over the one-year follow-up period, 22 patients (34.4%) had a poor prognosis: 5 subjects died and 17 subjects were either hospitalized or admitted to a nursing home. Of these 22 subjects with a poor prognosis, 8 subjects (36.4%) had OH, which tended to be higher than those in the favorable prognosis group ($p=0.3$). Among the 5 subjects who died, OH was present in 60.0%. Thus, the presence of OH appeared to be associated with a higher mortality compared with those without OH ($p=0.08$). The BP change within 3 minutes of standing was significantly greater in subjects with a poor prognosis (BP $18\pm 18/4\pm 8$ mmHg) than in those with a favorable prognosis ($5\pm 15/-1\pm 7$ mmHg) ($p<0.05$) (Fig. 3). Although no CV disease occurred among the subjects with a poor prognosis, one had a malignant tumor, 3 had infections (pneumonia, cholecystitis), 3 had fractures, 12

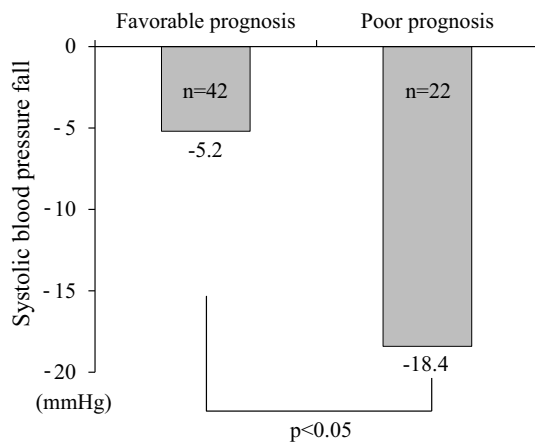


Figure 3. Relationship between the prognosis and decreases in the systolic blood pressure.

had worsening of activity of daily living and 3 had other non-CV events (chronic subdural hematoma or asphyxiation). Of these 22 subjects with a poor prognosis, 19 subjects had AD, 2 subjects had VaD and 1 subject had DLB. The event-free survival rate tended to be lower in subjects with OH than in those without OH ($p=0.3$), but the difference did not reach statistical significance (Fig. 4). The prognosis was not associated with the time on the TUG test or DM (data not shown).

Discussion

In the present study, we found that the number of subjects with OH was 26.6% of elderly patients with dementia who visited a hospital for daycare. The presence of OH was associated with a higher supine BP and faster time on the TUG test compared with those without OH, while OH was not related to the use of antihypertensive drugs, the MMSE score or the presence of DM. The prevalence of OH is reported to increase in an age-dependent manner with a prevalence of 4-6% in the middle-aged adult population (6, 8, 9, 18) and 7-34% in individuals 65 years of age and older (7, 13-17). It has been shown that frailty is a risk factor for OH. We demonstrated that OH is most pronounced immediately after standing, and the frequency of OH was high in individuals with higher supine SBP. It is known that hypertension is associated with OH (4), particularly in elderly people. One of the most important mechanisms of OH is baroreflex dysfunction, which is in part caused by baroreceptor impairment due to aging or atherosclerosis (23, 24). When we used the TUG test as a measure of physical function, we found that OH was associated with a shorter time on the TUG test, with whom physical function may be relatively preserved. Masaki et al. reported the relationship between OH and three generally accepted measures of physical frailty [longer timed 10-foot walk, weaker hand-grip strength, and lower FEV₁ (forced expiratory volume in one second)] (16). The reasons for the discrepant results between our study and the previous observations re-

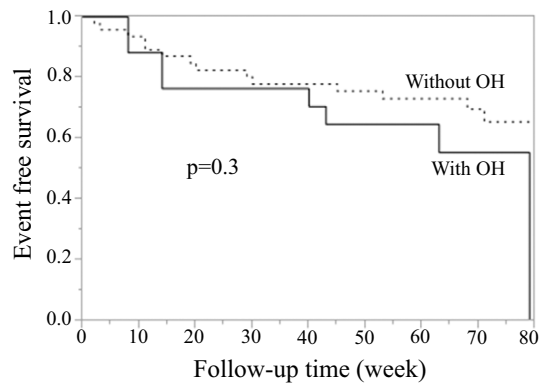


Figure 4. Kaplan-Meier curves of the one-year event-free survival rate in the subjects with and without orthostatic hypotension.

main to be determined, but may include the difference in the characteristics of the study subjects, i.e., our study subjects were older and suffered from dementia. Another possibility is that elderly dementia patients with preserved physical function could stand up quickly, thereby exhibiting immediate OH. Further studies are needed to test this possibility.

Previous reports have shown a significant association between OH and the cognitive function of elderly subjects (12, 13). Because we studied a group of dementia patients, the high prevalence of OH may not be surprising. However, the causal relationship between OH and the cognitive function has not been established.

OH is related to a higher prevalence of multiple silent cerebral ischemias and cerebrovascular damage, such as stroke and transient ischemic attack (25). It appears possible that OH per se may lead to cerebrovascular damage and could be a risk for cognitive decline. We are unable to address from the present study whether OH is a cause or a consequence of dementia.

According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension, treatment of hypertension is also recommended in elderly hypertensive people, including those over 80 years of age and those with dementia (26-28). Previous reports have shown that among faster walkers, those with elevated SBP (>140 mmHg) had a greater risk of mortality compared with those with SBP less than 140 mmHg (29). Considering the present observation that the subjects with OH showed higher supine SBP, the indications for antihypertensive treatment should be carefully judged by evaluating postural changes in BP.

In this study, the subjects with poor outcomes, as judged by the quality of life, hospitalization and mortality, had a higher rate of OH compared with those with a favorable prognosis, although the event-free survival rate did not reach statistical significance between those with and without OH. Evidence is accumulating to show that OH is associated with a higher risk of future mortality (7, 8, 16-18), although the previous results have not been consistent (30, 31). One meta-analysis indicated that subjects with OH were associated with a 40% higher risk of future all-cause mortal-

ity (32). One previous report has shown that orthostatic BP variability may be a better indicator of future stroke than a single supine or orthostatic change measure (33). In the present study, the orthostatic BP drop was significantly greater in subjects with a poor prognosis than in those with a favorable prognosis. We examined the risks associated with orthostatic systolic BP variability in older subjects. Our findings raised the possibility that the association between the presence of OH and future higher mortality may also be applied to elderly subjects with dementia. The mechanisms contributing to the high prevalence of OH in subjects with poor outcomes are not fully understood. Several suggested hypotheses may explain this association. First, several epidemiological studies have reported that OH was related to several classic risk factors for CV diseases and mortality, such as aging, hypertension, DM and chronic kidney disease (4-11, 15). Therefore, OH may lead to a higher mortality risk, partially through the impact of these classic risk factors. Second, subjects with OH are likely to have increased BP variability related to body posture, and a large proportion of the thoracic blood volume may be displaced to the lower limbs due to gravity during orthostasis, which may lead to serious ischemia of important organs, such as the heart, brain and kidney (32). Third, baroreflex dysfunction, a marker of autonomic nervous system imbalance implicated in the pathogenesis of OH, is characterized by enhanced sympathetic activity and the withdrawal of parasympathetic control and has been well recognized to be an important mediator of increased cardiovascular morbidity and mortality (34-36). These facts suggest that the association between OH and increased risk of death may at least partially be explained by potential autonomic dysfunction, and OH may be a marker of impaired autonomic CV regulation.

There are several limitations associated with this study. First, our findings are limited to elderly patients with dementia who visited a hospital for daycare. Our sample size was small, and thus, further studies with a larger sample size and comparisons between an appropriately-aged control group are needed, especially to elucidate whether elderly patients with dementia and OH have a poorer prognosis compared with those without dementia but with OH. This may merit further investigation in the face of growing numbers of elderly subjects with dementia in the general population (37). Second, it has been suggested that the reproducibility of OH is low and the frequency may vary during the day. Therefore, multiple examinations are desirable to establish a diagnosis of OH. Third, OH is most pronounced immediately after standing. However, the amount of time required to change the posture from the supine to standing position varied considerably among the study participants. We should therefore consider such differences in time required for postural changes. Fourth, because in this study the event-free survival rate did not significantly differ between those with and without OH, it remains to be clarified whether a high prevalence of OH in the poor outcome groups played a causal role in their outcome. Thus, our findings should be

interpreted within the context of these limitations.

In conclusion, the present findings demonstrated that OH is common in frail elderly subjects with dementia. Furthermore, OH appeared to be more prevalent in subjects with a poor prognosis. Thus, subjects complicated with dementia and OH should be carefully followed up in order to prevent any future events.

Author's disclosure of potential Conflicts of Interest (COI).

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