Original Article

Tilting-Induced Decrease in Systolic Blood Pressure in Bedridden Hypertensive Elderly Inpatients: Effects of Azelnidipine

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The object of this study was to examine blood pressure (BP) variability due to postural change in elderly hypertensive patients. The subjects studied were 154 elderly inpatients in a hospital for the elderly (48 male and 106 female; median age: 82 years), consisting of age- and sex-matched bedridden (*n*=39) and non-bedridden (*n*=39) normotensive controls and bedridden (*n*=38) and non-bedridden (*n*=38) hypertensive patients. BP and pulse rate (PR) were measured in the supine position, then again after a 2-min, 45 deg head-up tilt with the legs horizontal. The decrease in systolic BP (SBP) on tilting in the bedridden hypertensive group (median: −10 mmHg; range: −32 to 9 mmHg) was significantly ($p<0.008$) greater than those in the other three groups. Monotherapy with azelnidipine, a long-acting calcium channel blocker, for 3 months not only significantly reduced the basal BP and PR of hypertensive patients in the two groups, but also significantly ($p<0.05$) attenuated the tilt-induced decrease in the SBP to −3 mmHg (−19 to 25 mmHg) and enhanced the change in PR from −1 bpm (−10 to 7 bpm) to 1 bpm (−4 to 23 bpm) in the bedridden hypertensive group. Our findings indicate that tilt-induced decrease in SBP is a rather common phenomenon in bedridden elderly hypertensive patients, and that treatment with azelnidipine attenuates tilt-induced decrease in SBP, probably through an improvement of baroreceptor sensitivity. (*Hypertens Res* 2006; 29: 943–949)

***Key Words*: bedridden, head-up tilt, systolic blood pressure, hypertensive elderly, azelnidipine**

Introduction

Increased blood pressure (BP) variability on postural change is a recognized feature in the elderly, especially in those with hypertension (*1*). Moreover, many longitudinal epidemiological studies have shown that increased BP variability on postural change is associated with future cardiovascular events, including coronary heart disease (*2*), stroke (*3*), and even mortality (*4*), and is also recognized as a risk factor for cognitive impairment (*5*) and silent cerebrovascular disease (*6*). In addition, it has recently been reported that lying in a prone posture can lead to unregulated postural hypotension, which has the possibility of being a novel predictor of cardiovascular disease (*7*).

On the other hand, tilting-up of the upper body with the legs horizontal is a commonly performed maneuver in bedridden elderly subjects, and may prevent aspiration pneumonia (*8*).

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Table 1. Comparison of Clinical Factors among Normotensive and Hypertensive Inpatients with Non-Bedridden and Bedridden States in a Geriatric Hospital

	NB elderly (n=77)		B elderly (n=77)	
	N (n=39)	H (n=38)	N (n=39)	H (n=38)
Clinical background				
Age (years)	83 (72–93)	82 (70–93)	83 (71–91)	82 (70–92)
Male/female	12/27	12/26	12/27	12/26
Chronic conditions (n (%))				
Dementia	12 (30.8)	11 (28.9)	29 (74.4)$^{\dagger,\#}$	32 (84.2)$^{\dagger,\#}$
Stroke	7 (17.9)	9 (23.7)	29 (74.4)$^{\dagger,\#}$	22 (57.4)$^{\dagger,\#}$
Ischemic heart disease	4 (10.3)	11 (28.9)	8 (20.5)	9 (23.7)
Congestive heart failure	4 (10.3)	4 (10.5)	6 (15.4)	2 (5.3)
Hypoalbuminemia	5 (12.8)	0 (0.0)	11 (28.2)$^{\#}$	6 (15.8)
Diabetes mellitus	0 (0.0)	3 (7.9)	2 (5.1)	0 (0.0)

Values are expressed as median (range) in age. N, normotensives; H, hypertensives; NB, non-bedridden; B, bedridden. $^{\dagger}p<0.008$, *vs*. NB-N group. $^{\#}p<0.008$, *vs*. NB-H group.

However, little has been reported about the BP variability in completely bedridden elderly inpatients. In the present study, we compared variability of BP and pulse rate (PR) at the time of tilting-up of the upper body in non-bedridden and bedridden inpatients with and without hypertension in a hospital for the elderly. We also examined the effects of azelnidipine, a newly developed dihydropyridine-type calcium antagonist that acts without augmentation of the sympathetic nervous system (*9*, *10*), on variability of BP and PR in these hypertensive elderly inpatients.

Methods

Study Subjects

The study was conducted in Sengi-Hospital, a geriatric hospital serving as both a hospital and a long-term care facility for the elderly, which is a common combination of medical and care services in Japan (*11*). Katz's activities of daily living (ADL: bathing, dressing, going to the toilet, transfer, continence, feeding) (*12*) and the Braden scale (*13*) were assessed once a month in all inpatients in the hospital. The research protocol was approved by the Ethics Committee of the hospital. Patients aged 70 years and older, all of whom were Japanese with an admission period of 16 weeks or longer, were invited to participate in the study. All residents who gave informed consent (or whose family members gave consent) were enrolled. Both normotensive and hypertensive subjects were selected from bedridden residents. Control normotensive and hypertensive subjects were age- and sex-matched random samples of non-bedridden subjects admitted to the same hospital. The computerized admission lists served as the sampling frame, and we frequency matched the controls to the cases by sex and age (within ±2 years) at a ratio of 1:1. Hypertension was defined as systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg measured in the supine position. Patients were defined as bedridden if they showed dependency in all sub-items in Katz's ADL (*12*), in addition to being permanently confined to bed (score: 1 or 2) according to the sub-item of "activity" score in the Braden scale (*13*). Patients were defined as non-bedridden if they showed independence in all of Katz's ADL items (*12*). None of the subjects had had any antihypertensive treatment for 2 months prior to enrollment. We excluded 1) subjects admitted to the hospital or at the start of the investigation with clinical diagnoses of Parkinsonism (*14*), Shy-Drager syndrome (*15*), amyloidotic polyneuropathy (*16*), or vitamin B_{12} deficiency (*17*); 2) subjects treated with any drug that may have contributed to or decreased the likelihood of orthostatic hypotension, such as diuretics, α-blockers or β-blockers; 3) subjects considered critically ill (*18*); 4) postoperative patients; and 5) patients admitted for less than 16 weeks.

Procedure for Modified Head-Up Tilt

Basal BP and PR of the elderly subjects were determined by averaging two determinations of supine BP measured with an automatic cuff-oscillometric BO recorder (HEM-705CP; OMRON Co., Ltd., Kyoto, Japan) after the subjects had rested for more than 30 min in the morning before breakfast. The responses of BP and PR were analyzed after a 2-min, 45 deg head-up tilt with the legs horizontal (0 deg) according to the procedure of Gotshall *et al*. (*19*). BP and PR were measured 2 min after the postural change (*20*). Tilt-induced hypotension was defined as a fall in SBP of 20 mmHg or greater and/or DBP of 10 mmHg or greater according to the consensus statement on the definition of orthostatic hypotension (*21*). The changes in BP and PR with the same head-up

Table 2. Comparison of Blood Pressure and Heart Rate at Time of Modified Head-Up Tilt among Normotensive and Hypertensive Inpatients with Non-Bedridden and Bedridden States in a Geriatric Hospital, and between before and after Azelnidipine Treatment

	NB elderly (n=77)		B elderly (n=77)	
	N (n=39)	H (n=38)	N (n=39)	H (n=38)
Before treatment				
Basal supine position				
Systolic BP (mmHg)	122 (106–136)	155 (139–199)†	119 (92–138)$^{\#}$	155 (146–203)$^{\dagger,\#}$
Diastolic BP (mmHg)	70 (54–89)	79 (64–97)†	72 (37–88)$^{\#}$	81 (58–100)$^{\dagger,\#}$
Heart rate (/min)	71 (53–86)	68 (58–86)	75 (58–106)	78 (56–114)
2 min after head-up tilt				
Systolic BP (mmHg)	124 (105–136)	165 (125–188)†	118 (94–162)$^{\#}$	151 (115–199)$^{\dagger,\#}$
Diastolic BP (mmHg)	72 (52–87)	82 (57–105)†	73 (51–93)$^{\#}$	81 (52–132)
Heart rate (/min)	67 (52–85)	66 (52–91)	74 (58–106)	76 (58–99)
Azelnidipine treatment				
Basal supine position				
Systolic BP (mmHg)	—	124 (108–168)$^{\$}$	—	133 (110–170)$^{\$}$
Diastolic BP (mmHg)	—	76 (63–99)$^{\$}$	—	81 (60–91)$^{\$}$
Heart rate (/min)	—	68 (49–86)	—	69 (45–89)$^{\$}$
2 min after head-up tilt				
Systolic BP (mmHg)	—	129 (114–174)$^{\$}$	—	130 (104–162)$^{\$}$
Diastolic BP (mmHg)	—	76 (57–98)$^{\$}$	—	79 (61–90)
Heart rate (/min)	—	69 (51–86)	—	72 (50–93)

Values are expressed as median (range). BP, blood pressure; N, normotensives; H, hypertensives; NB, non-bedridden; B, bedridden; —, no data. $^{\dagger}p<0.008$, *vs*. NB-N group. $^{\#}p<0.008$, *vs*. NB-H group. $^{\$}p<0.05$, *vs*. before treatment with azelnidipine in the same situation in NB-H or B-H groups.

tilt were also determined at 3 months after the start of administration of azelnidipine at a dose of 4 to 16 mg/day.

Data Collection

Operational definitions of each pre-existing potential risk factor for autonomic dysfunction, including stroke (motor deficit and evidence of cerebral hemispheric infarction on computed tomography and/or magnetic resonance imaging) (*22*, *23*), dementia (Mini-Mental State Examination score ≤23) (*17*), chronic ischemic heart disease (previous myocardial infarction or angina pectoris) (*24*), congestive heart failure (left ventricular ejection fraction <40% on echocardiography) (*25*), hypoalbuminemia (serum albumin level <30 g/l) (*26*), and diabetes mellitus (treated with insulin, oral hypoglycemic agent, or fasting blood glucose ≥7 mmol/l) (*26*, *27*), were established prior to data collection. Data were retrieved from medical records before the start of the examination. Personal physicians were involved in the diagnoses of these complications, which were further evaluated by a committee. Objective and routinely collected medical information was applied to augment the diagnostic accuracy. Only chronic conditions were recorded for the cases and respective controls.

Statistical Analyses

Data are expressed as the median and full range. The data were analyzed by Kruskal-Wallis χ^2 and Mann-Whitney U analysis as a multiple comparison using post hoc Bonferroni correction. p values were set at 0.008. Differences in changes of BP and PR by treatment with azelnidipine were assessed by nonparametric Wilcoxon test, and a value of $p<0.05$ was regarded as significant. Data were analyzed on a microcomputer running SPSS version 12 (SPSS, Chicago, USA).

Results

Clinical Characteristics of the Four Groups of Elderly Inpatients

Clinical characteristics of the subjects are shown in Table 1. Numbers of non-bedridden (NB) and bedridden (B) normotensive (N) elderly subjects were 39 (each 12 male and 27 female) and NB and B hypertensive (H) elderly subjects were 38 (each 12 male and 26 female). The median age was not significantly different among the four groups. The prevalence of dementia and chronic phase of stroke in the two bedridden groups (B-N and B-H) was significantly higher than that in

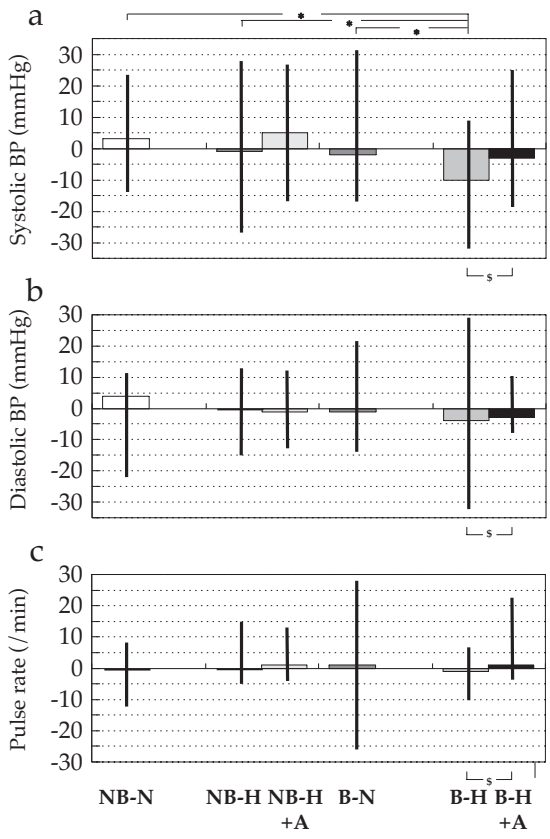

Fig. 1. *Changes in systolic blood pressure (SBP) (a) and diastolic blood pressure (DBP) (b) values and pulse rate (c) at 2 min after head-up tilt from the initial supine position in the four groups. Columns and bars represent the medians and full ranges in each group. NB-N, non-bedridden normotensive group; NB-H, non-bedridden hypertensive group; B-N, bedridden normotensive group; and B-H, bedridden hypertensive group. +A, after treatment with azelnidipine in groups NB-H and B-H.* *p < *0.008* vs. *the NB-H group.* $p < *0.05* vs. *before treatment with azelnidipine after the same maneuver in the NB-H or B-H groups.*

the non-bedridden groups (NB-N and NB-H), respectively, and the prevalence of hypoalbuminemia in the B-N group was significantly higher than that in the NB-H group (Table 1).

Changes in BP and PR by Modified Tilt in the Four Groups

Values in SBP, DBP, and PR at the basal supine position and at 2 min after the modified tilt are summarized in Table 2. Both the SBP and DBP values in the two hypertensive groups were significantly higher than those in the two normotensive groups, with the exception that the DBP in the B-H group at 2 min after the tilt was not significantly different from those of the other three groups.

Figure 1 summarizes the changes in SBP and DBP values and PR at 2 min after head-up tilt from the initial supine position in the four groups. Decreases in SBP in the B-H group (median: −10 mmHg; range: −32 to 9 mmHg) were significantly greater than those in either the NB-N group (4 mmHg, −14 to 24 mmHg, $p<0.001$), NB-H group (−1 mmHg, −26 to 28 mmHg, $p=0.001$) or B-N group (−2 mmHg, −17 to 31 mmHg, $p=0.001$), respectively.

On the other hand, the numbers of subjects with tilt-induced hypotension were not significantly different among the NB-N ($n=7$), NB-H ($n=6$), B-N ($n=5$), and B-H ($n=10$) groups by the Kruskal-Wallis test.

Effects of Azelnidipine on BP Change Induced by Head-Up Tilt

Treatment with azelnidipine, a new calcium channel blocker, not only significantly ($p<0.05$) decreased the SBP and DBP levels in the two groups, but also significantly attenuated the higher basal PR in the B-H group to a value comparable to that in the NB-N group (Table 2). Moreover, azelnidipine not only attenuated the tilt-induced prominent decrease in SBP observed before treatment of patients in the B-H group to a level comparable to that in the B-N group, but also significantly enhanced the tilt-induced change in PR to a value comparable to those in the other groups (Fig. 1).

All 10 patients with tilt-induced hypotension in the B-H group were assessed as not having hypotension after the treatment with azelnidipine ($p=0.003$), with significant increments in the tilt-induced changes in SBP (median, −20 mmHg, and range, [−32 to −7 mmHg], before the treatment; to −11 mmHg [−19 to 3 mmHg] after the treatment; $p=0.008$), in DBP (−10 mmHg [−32 to −7 mmHg] to −3 mmHg [−8 to 2 mmHg]; $p=0.005$), and in PR (−1 bpm [−10 to 7 bpm] to 0 bpm [−4 to 23 bpm]; $p=0.024$). Although administration of azelnidipine to the remainder of the 28 patients without tilt-induced hypotension in the B-H group also significantly enhanced the tilt-induced changes in SBP (−4 mmHg [−18 to 9 mmHg] to −2 mmHg [−16 to 25 mmHg]; $p=0.0014$) and in PR (0 bpm [−3 to 7 bpm] to 1 bpm [−1 to 6 bpm]; $p<0.001$), the increment in tilt-induced change in DBP (−1 mmHg [−9 to 5 mmHg] to 1 mmHg [−8 to 10 mmHg]) was not significant ($p=0.210$). Although 4 out of 6 patients with tilt-induced hypotension in the NB-H group were judged not to have hypotension after the treatment with azelnidipine, this difference was not statistically significant ($p=0.157$). Mann-Whitney U analysis and χ^2 analysis did not reveal any significant difference in the mean age or prevalence of the clinical factors, including male gender, dementia, stroke, ischemic heart disease, congestive heart failure, hypoalbuminemia, diabetes mellitus, or bedridden itself, between the 14 hypertensive elderly subjects (4 in the NB-H group and 10 in the B-H group) who showed improvement of the postural hypotension by azelnidipine and the 2 subjects in the NB-H group without the improvement.

Discussion

Our study demonstrated a greater decrease in SBP in the B-H group compared to the other three groups by a quite commonly used nursing maneuver of 45 deg head-up tilt with the legs horizontal. A greater decrease in BP by the head-up tilt is often seen in elderly hypertensive patients (*28*), and is caused by retarded sympathetic nerve activation mainly due to impaired baroreflex sensitivity (*28*), which cannot adjust decreases in cardiac output and arterial pressure due to redistribution of blood from the thoracic area to the deep intra- and inter-muscular vein of the legs by the tilt stress (*29*). The impaired baroreflex activation in these elderly hypertensive patients is represented at least in part by an inadequately lower increment in baroreflex-mediated PR despite a greater decrease in BP compared to that in normotensive elderly subjects (*30*). The elderly B-H patients in this study were characterized by a decrement of the median PR despite a significant decrement of SBP at the time of the tilt, which may be an ultimate feature of autonomic impairment (Fig. 1), suggesting that impaired baroreflex activation played a role in the prominent decrease in SBP in response to the head-up tilt in the B-H patients. On the other hand, increments in both SBP and DBP in response to head-up tilt were observed in NB-N subjects. This value was comparable to that in young normal subjects at the time of head-up tilt in a previous report (*28*). These findings suggest that normotensive healthy subjects, even at a very old age, show a normal autonomic response to the tilt stress, similar to that in young normal subjects.

In the present study, all the patients in the NB-H and B-H groups were treated with azelnidipine, a newly developed dihydropyridine-type calcium channel antagonist with a slowly developing and long-lasting hypotensive effect characterized by little reflex tachycardia (*9*, *10*, *31*). Treatment with azelnidipine not only significantly decreased basal SBP and DBP in patients in both hypertensive groups, but also significantly attenuated the higher basal PR of patients in the B-H group to a level comparable to that of subjects in the NB-N group (Table 2). This observation is partly compatible with a previous report that azelnidipine significantly decreased PR on 24-h ambulatory monitoring (*9*). Despite the significant decreases in BP and basal PR in the B-H patients, azelnidipine not only significantly attenuated the decrements of both SBP and DBP but also reversed the decrement of PR in response to the tilt (Fig. 1). Moreover, all the hypertensive patients with tilt-induced hypotension in the B-H group were judged as not having hypotension after the treatment with azelnidipine. In addition, these patients showed even greater attenuations of the tilt-induced decrements in SBP and DBP compared to those who were originally diagnosed as not having tilt-induced hypotension in the same group, although we used a rather strict criterion for the definition of tilt-induced hypotension—namely, a 20/10 mmHg or greater decline at the time of tilting compared to the spine BP, which is the criterion for orthostatic hypotension (*32*). These observations indicate that the augmenting effect of azelnidipine on the retarded sympathetic nerve activation was more effectively exerted on elderly B-H subjects who showed more severe decreases in BP by the postural change.

Although many antihypertensive agents are known to improve orthostatic hypotension in elderly hypertensive patients (*33*), the associations between dihydropyridine-type calcium blockers and postural hypotension are rather complicated: calcium blockers themselves sometimes induce postural hypotension (*34*), or have no effect on postural hypotension (*35*). Ferodipine (*36*, *37*) and nifedipine (*33*) even attenuate orthostatic hypotension. However, our study is the first to show a high prevalence of postural hypotension in long-term bedridden hypertensive elderly subjects, and the first to show an azelnidipine-induced improvement in postural hypotension among these subjects. The precise mechanism(s) by which azelnidipine improves the head-up-tilt–induced decreases in BP, especially in elderly B-H patients, is unknown. However, unlike in the case of most other long-acting dihydropyridine calcium channel antagonists, the antihypertensive efficacy of azelnidipine is characterized not only by an absence of reactive tachycardia, but also by suppressing effects on sympathetic nervous activity (*9*, *10*, *31*). The additive beneficial effects of the combination of azelnidipine and an angiotensin blocker have recently been described in a hypertensive rat-heart failure model (*38*). On the other hand, the sympathetic nervous activities in astronauts on the 12th and 13th spaceflights during the Neurolab space shuttle mission were actually enhanced compared to the pre-flight levels (*39*). According to these findings as well as the results on the recording of sympathetic nervous activity in subjects exposed to ground-based short- and long-term "stimulations" of microgravity induced by head-down tilt, Mano (*40*) reported that sympathetic neural control was lowered when subjects were exposed to short-term microgravity for several hours, but was enhanced after exposure to long-term microgravity for more than 3 days. In addition, he reported that the orthostatic intolerance based on impaired baroreflex functions in these subjects may have resulted from an exhaustion of the sympathetic nervous system by prolonged exaggerated sympathetic activity after exposure to long-term microgravity stress. He also indicated that the autonomic dysfunctions seen in bedridden subjects may be medicated by the same mechanism (*40*). Based on these observations, the beneficial effect of azelnidipine on the postural hypotension observed especially in elderly B-H patients may be the result of the augmenting effect of azelnidipine on baroreflex sensitivity through a suppression of the exaggerated sympathetic activity due to long-term microgravitational stress. It is also possible that the enhancing effect of azelnidipine on blood flow of the brain (*41*) may have contributed to the improvement of tilt-induced hypotension, since postural hypotension is associated with ischemic change in the brain on magnetic resonance imaging, such as periventricular white matter hyperintensity,

in older elderly subjects (*5*).

In the present study, we did not evaluate hemodynamic or humoral factors, such as echocardiographic measurements and circulating levels of catecholamines and factors associated with the renin-angiotensin-aldosterone system, at the time of tilting. We also did not estimate baroreflex function. These factors should be measured in the future to elucidate the beneficial effects of azelnidipine.

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