Original Article

Impact of Blood Pressure Variability on Cardiovascular Events in Elderly Patients with Hypertension

Masato ETO, Kenji TOBA, Masahiro AKISHITA, Koichi KOZAKI, Tokumitsu WATANABE, Seungbum KIM, Masayoshi HASHIMOTO, Junya AKO, Katsuya IIJIMA, Noriko SUDOH, Masao YOSHIZUMI, and Yasuyoshi OUCHI

Blood pressure variability is one of the characteristic features of hypertension in the elderly. However, its clinical significance remains to be determined. We therefore examined the impact of blood pressure variability on the development of cardiovascular events in elderly hypertensive patients. A total of 106 consecutive hypertensive patients aged more than 60 years old (mean age, 73.9±8.1 years old; male, 54%), all of whom underwent 24-h ambulatory blood pressure monitoring, were followed up (median, 34 months; range, 3–60 months). During the follow-up period, 39 cardiovascular events were observed, including 14 cases of cerebral infarction and 7 cases of acute myocardial infarction. The coefficient of variation (CV) of 24-h systolic blood pressure (SBP) values was used as an index of blood pressure variability. The patients showed a mean CV value of 10.6%, and were divided into two groups according to this mean value as a cut-off point: a high CV group (n=46) and a low CV group (n=60). Although baseline clinical characteristics were similar in the two groups, Kaplan-Meier plots for event-free survival revealed that the rate of cardiovascular events was significantly higher in high CV group than in low CV group (p<0.05). Cox's proportional hazards analysis showed that increased blood pressure variability (a high CV value of 24-h SBP) was an independent predictive variable for cardiovascular events. The CV value of daytime SBP and the SD value of both 24-h SBP and daytime SBP also had positive correlations with the onset of cardiovascular events. These results suggest that increased blood pressure variability may be an independent risk factor for cardiovascular events in elderly hypertensive patients. (*Hypertens Res* 2005; 28: 1–7)

***Key Words*: elderly hypertension, blood pressure variability, cardiovascular events, ambulatory blood pressure monitoring**

Introduction

Hypertension has been well established as a major predisposing factor for cardiovascular disease (*1*). The goal of treatment for hypertensive patients is not only to reduce blood pressure, but also to prevent cardiovascular events. The prevalence of hypertension increases with age (*2*), and elderly hypertensive patients are known to have some specific clinical features, such as isolated systolic hypertension (*3*), blood pressure variability (*4*, *5*), orthostatic hypotension (*6*, *7*) and postprandial hypotension (*8*).

Blood pressure variability is a characteristic feature of hypertension in the elderly (*4*, *5*). The arterial baroreflex

From the Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.
This work was supported in part by a Grant-in-Aid (No. 08670768) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.
Address for Reprints: Yasuyoshi Ouchi, M.D., Ph.D., Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, 7–3–1 Hongo, Bunkyo-ku, Tokyo 113–8655, Japan. E-mail: youchi-tky@umin.ac.jp
Received January 19, 2004; Accepted in revised form August 20, 2004.

Table 1. Baseline Clinical Characteristics

	Total (n=106)	Low CV group (n=60)	High CV group (n=46)	p value
Age (years old; mean±SD)	73.9±8.1	74.4±7.9	73.2±8.3	NS
(range)	(60−91)	(60−91)	(60−87)	
Sex (men) (n (%))	58 (54%)	36 (60%)	22 (48%)	NS
WHO class (n (%))				
I	31 (29%)	22 (37%)	9 (20%)	NS
II	22 (21%)	12 (20%)	10 (22%)	
III	53 (50%)	26 (43%)	27 (58%)	
Smoking (n (%))	53 (50%)	32 (53%)	21 (46%)	NS
Antihypertensive drug (n (%))				
ACE inhibitor	19 (18%)	10 (17%)	9 (20%)	NS
β-Blocker	7 (7%)	4 (7%)	3 (7%)	
Ca channel blocker	82 (77%)	48 (80%)	34 (74%)	
Diuretics	13 (12%)	8 (13%)	5 (11%)	
Complicaton (n (%))				
Hypercholesterolemia	33 (31%)	21 (35%)	12 (26%)	NS
Diabetes	36 (34%)	22 (37%)	14 (30%)	NS
Cerebrovascular disease	32 (30%)	19 (32%)	13 (28%)	NS
Coronary artery disease	19 (18%)	9 (15%)	10 (22%)	NS
Total cholesterol (mg/dl; mean±SEM)	189.5±12.2	180.5±13.3	209.1±11.4	NS
Creatinine (mg/dl; mean±SEM)	1.0±0.1	0.9±0.1	1.0±0.1	NS

CV, coefficient of variation; ACE, angiotensin converting enzyme.

plays a pivotal role in the neural regulation of blood pressure, and blood pressure variability is regulated by this compensatory reflex mechanism. Arterial baroreflex function is decreased in elderly individuals (*9*, *10*), and as a result, their blood pressure fluctuates (*11*). Although the mechanism of blood pressure variability in the elderly has been well elucidated, its clinical significance remains to be determined. In particular, there is little available information on the relationship between blood pressure variability and cardiovascular events in elderly hypertensive patients.

We hypothesized that blood pressure variability would be an independent risk factor for cardiovascular events in elderly patients with hypertension. To test this hypothesis, we investigated the outcome of elderly patients who underwent ambulatory blood pressure monitoring (ABPM). The results demonstrated that increased blood pressure variability is an independent predictive variable for cardiovascular events.

Methods

Patients

We recruited a total of 106 consecutive hypertensive patients, aged 60 years or older, who underwent 24-h ABPM at the University of Tokyo Hospital. The age, sex, smoking status, World Health Organization/International Society of Hypertension (WHO/ISH) classification, presence or absence of hypercholesterolemia and diabetes, history of cerebrovascular disease and history of coronary artery disease of each patient were investigated as baseline clinical characteristics according to their medical records. Hypertension was defined as an office systolic blood pressure (SBP) level above 140 mmHg and/or an office diastolic blood pressure (DBP) level above 90 mmHg on more than two occasions or the use of antihypertensive drugs. Smokers were defined as current smokers. Hypercholesterolemia was defined as a serum total cholesterol concentration above 220 mg/dl or the use of lipid-lowering drugs. Diabetes mellitus was defined as a fasting plasma glucose concentration above 140 mg/dl or use of antidiabetic medication. None showed severe renal failure (serum creatinine>2.0 mg/dl). Informed consent for this study was obtained from all patients.

Twenty-Four-Hour ABPM

Ambulatory blood pressure was recorded with a noninvasive automatic ABPM device (ABPM-630; Nippon Colin, Komaki, Japan) every 30 min for 24 h. The data used in this study were obtained by the oscillometric method. The accuracy of this device was previously described (*12*). Patients were not included in the study if their blood pressure could not be evaluated because of artifacts in more than 10% of the total measurements.

The mean values of 24-h, daytime (from 6:00 to 21:00) and nighttime (from 21:30 to 5:30) SBP and DBP were calculated for each patient. We calculated the coefficient of variation

Table 2. Profiles of 24 h, Daytime, Nighttime and Casual Blood Pressure

	Total (n=106)	Low CV group (n=60)	High CV group (n=46)
24 h blood pressure			
Systolic blood pressure (mmHg)	142.4±17.2	143.3±17.2	141.2±16.6
Diastolic blood pressure (mmHg)	78.1±10.3	79.2±10.6	76.8±9.9
CV of systolic blood pressure (%)	10.6±2.9	8.8±1.4	13.1±2.5*
Daytime blood pressure			
Systolic blood pressure	143.7±17.0	143.9±17.2	141.9±16.5
Diastolic blood pressure (mmHg)	79.2±10.4	79.7±10.9	78.6±9.9
Nighttime blood pressure (mmHg)			
Systolic blood pressure (mmHg)	140.1±20.3	142.0±18.5	137.7±20.7
Diastolic blood pressure (mmHg)	75.2±11.3	77.0±11.1	73.0±11.4
Casual blood pressure			
Systolic blood pressure (mmHg)	148.7±19.1	150.5±15.5	146.0±22.8
Diastolic blood pressure (mmHg)	81.4±11.6	82.0±10.0	81.0±13.0
Pulse pressure (mmHg)	67.3±16.6	69.1±16.0	64.8±17.3

Data are expressed as mean±SD. CV, coefficient of variation. *$p<0.01$.

(CV; CV=SD/mean value 100%) of 24-h SBP as an index of blood pressure variability. The CV values of daytime SBP and nighttime blood pressure as well as the SD values of 24-h SBP, daytime SBP and nighttime blood pressure were also calculated. Casual blood pressure was measured by the standard cuff method in the morning (9:00 to 12:00) when the ambulatory blood pressure was monitored.

To confirm the reproducibility, we compared the two subsequent measurements in 23 patients who underwent 24-h ABPM twice within 1 month. There were significant positive correlations between the two measurements of 3 parameters of 24-h blood pressure (24-h SBP, $r=0.808$, $p<0.01$; 24-h DBP, $r=0.693$, $p<0.01$; CV of 24-h SBP, $r=0.564$, $p<0.01$, $n=23$).

Follow-Up

Patients were followed up in the outpatient clinic of the hospital. Cardiovascular endpoints consisted of new onset of angina pectoris, acute myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, sudden cardiac death, heart failure, cerebral infarction, cerebral hemorrhage, transient cerebral ischemic attack, acute aortic dissection and aortic graft replacement surgery for aortic aneurysm. Angina pectoris was diagnosed based on a history of chest pain and reversible ischemic change on electrocardiography during a spontaneous attack or exercise stress test. Acute myocardial infarction was diagnosed based on a history of chest pain, transient ST elevation on electrocardiography and increased serum myocardial enzyme concentrations. Sudden cardiac death was defined as a death that occurred within 1 h after the onset of symptoms. Heart failure was diagnosed based on clinical symptoms and signs and chest roentgenographic findings. Cerebral infarction and cerebral hemorrhage were diagnosed based on focal neurological deficits and brain computed tomographic findings. Transient cerebral ischemic attack was diagnosed based on focal neurological deficits that disappeared completely less than 24 h after the onset. Acute aortic dissection was diagnosed based on a history of chest, back and/or abdominal pain and thoracic and abdominal computed tomographic findings.

Data Analysis

To explore the clinical significance of blood pressure variability on cardiovascular events, we divided the patients into two groups: a high CV group and a low CV group, using the mean CV value of 24-h SBP (10.6%) as a cut-off point and compared the two groups in terms of baseline clinical characteristics, blood pressure profiles and the incidence of cardiovascular events. In addition, we divided the patients into two groups according to the mean values of CV of daytime and nighttime SBP and SD of 24-h, daytime and nighttime SBP and analyzed the data for each group. Data are expressed as the mean±SD. Categorical variables were compared by χ^2 test. Continuous variables were compared by Student's t-test. Kaplan-Meier curves were plotted for event free survival and compared by log rank test. Finally, Cox's proportional hazards analysis was performed to examine the relative risk for cardiovascular events using age, sex, WHO/ISH class, smoking, hypercholesterolemia, diabetes, history of cerebrovascular disease, history of coronary artery disease, mean 24-h blood pressure, mean daytime blood pressure, mean nighttime blood pressure, casual blood pressure, pulse pressure and CV (or SD) of SBP as variables. A value of $p<0.05$ was considered to be significant.

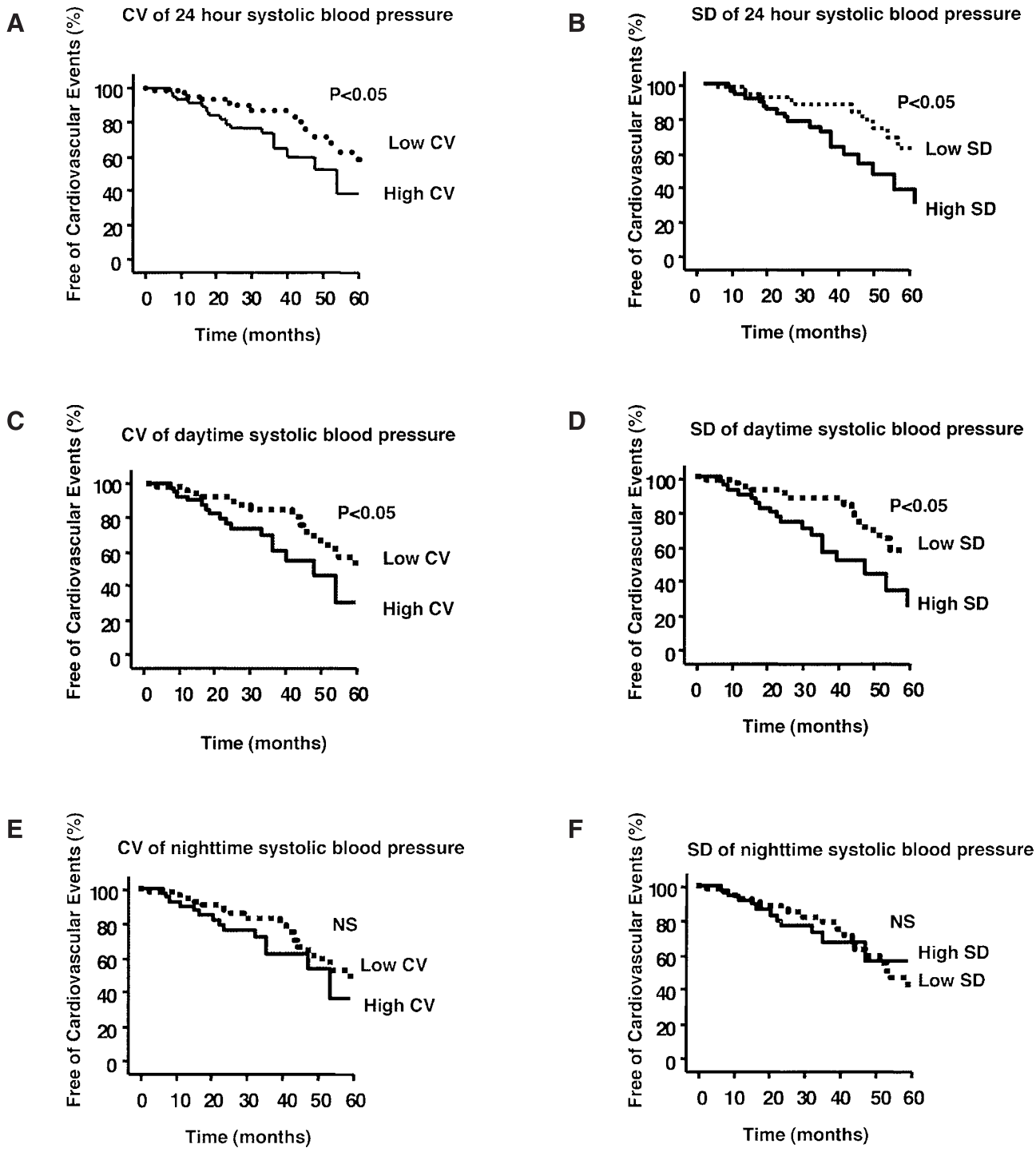

Fig. 1. *Cumulative event-free rates of cardiovascular events. Patients were divided into two groups according to the mean values of the CV of 24-h blood pressure (A), daytime blood pressure (C) or nighttime blood pressure (E), or those of the SD of 24-h blood pressure (B), daytime blood pressure (D) or nighttime blood pressure (F). CV, coefficient of variation.*

Results

The baseline clinical characteristics are shown in Table 1. All patients were treated with one or two antihypertensive drugs. Calcium channel blockers were used in 77% of the patients. ACE inhibitors, β-blockers and diuretics were used in 18%, 7% and 12% of the patients, respectively (Table 1). The

Table 3. Relative Risk of Cardiovascuiar Events

	Relative risk	95% CI
A		
Sex (male)	3.28	1.22–8.81*
24-h SBP (≥150 mmHg)	5.17	2.03–13.1**
CV of 24-h SBP (≥10.6%)	3.58	1.63–7.85*
B		
History of coronary artery disease	4.88	1.41–16.9*
24-h SBP (≥150 mmHg)	6.57	2.24–24.9*
SD of 24-h SBP (≥15.0 mmHg)	3.26	1.25–8.52*
C		
Sex (male)	3.22	1.14–9.09*
History of coronary artery disease	5.00	1.38–18.1*
24-h SBP (≥150 mmHg)	7.46	2.37–30.5*
CV of daytime SBP (≥11.4%)	3.72	1.08–15.1*
D		
History of coronary artery disease	4.94	1.41–18.1*
24-h SBP (≥150 mmHg)	6.63	2.23–25.8*
SD of daytime SBP (≥16.4 mmHg)	3.72	1.06–8.00*

Clinical characteristics, mean values of 24-h, daytime, nighttime and casual blood pressure, pulse pressure and SD of daytime, nighttime SBP are used as variables. *$p<0.05$, **$p<0.01$. CI, confidence interval; SBP, systolic blood pressure; CV, coefficient of variation.

results of ABPM and casual blood pressure measurement are summarized in Table 2. Table 1 shows that there were no significant differences between the two groups in baseline clinical characteristics, including the history of cerebrovascular disease and that of coronary artery disease. Table 2 shows that mean 24-h blood pressure, mean daytime blood pressure, mean nighttime blood pressure, casual blood pressure and pulse pressure were also similar between the two groups.

The median follow-up period was 34 months (range, 3–60 months). A total of 39 cardiovascular events occurred during the follow-up period. The events consisted of 3 cases of angina pectoris, 7 of acute myocardial infarction, 1 of coronary artery bypass graft surgery, 3 of sudden cardiac death, 3 of heart failure, 14 of cerebral infarction, 1 of cerebral hemorrhage, 5 of transient cerebral ischemic attack and 2 of aortic graft replacement surgery. Neither percutaneous coronary intervention nor acute aortic dissection was observed.

To investigate the impact of blood pressure variability on the onset of cardiovascular events, we plotted Kaplan-Meier curves for event-free survival and compared them between the two groups. Figure 1A shows that the rate of cardiovascular events was significantly higher in the high CV group than in the low CV group. When the patients were divided into two groups according to the mean value of SD of 24-h SBP, a significantly higher rate of cardiovascular events was observed in the high SD group (Fig. 1B). With respect to daytime SBP, patients with high CV values of daytime SBP as well as those with high SD values also had significantly more cardiovascular events (Fig. 1C, D). On the other hand, no difference in the rate of cardiovascular events was observed between the two groups when the mean value of CV or SD of nighttime SBP was used as a cut-off point (Fig. 1E, F).

To determine the independent predictive factors for cardiovascular events, the Cox's proportional hazards analysis was performed. This analysis identified male sex, high mean 24-h SBP and increased blood pressure variability (high CV value of 24-h SBP) as independent predictors for cardiovascular events (Table 3, A). In addition, the SD value of 24-h SBP was used as a variable rather than CV and the analysis was performed. History of coronary artery disease, high mean 24-h SBP and high SD value of 24-h SBP were significantly correlated with the onset of cardiovascular events (Table 3, B). Next, CV values of both daytime and nighttime blood pressure were used as variables. Male sex, history of coronary artery disease, high mean 24-h SBP and high CV value of daytime SBP were independent predictors (Table 3, C). Finally, the SD values of both daytime and nighttime blood pressure were used instead of the CV values and the analysis was performed. History of coronary artery disease, high mean 24-h SBP and high SD value of daytime SBP had significant correlations with the onset of cardiovascular events (Table 3, D).

Discussion

Hypertension is one of the leading causes of cardiovascular events (*1*) and the prevalence of hypertension increases with age (*2*). Therefore, it is important to clarify how to manage elderly hypertensive patients in clinical practice on the basis of their clinical features. Indeed, recent clinical trials have demonstrated that some antihypertensive drugs have a beneficial effect in elderly patients with isolated systolic hypertension (*13*, *14*). However, the clinical significance of blood pressure variability remains to be determined in elderly hypertensive patients. Therefore, in this study, we analyzed the relationship between blood pressure variability and cardiovascular events in those patients.

Many studies concerning the clinical values of blood pressure variability have focused on circadian rhythm (*15–23*). Very recently, several clinical studies have been published to clarify the significance of blood pressure variability (*24–31*). The degree of blood pressure variability is related to hypertensive target organ damage (*24*, *25*). The SD value of daytime blood pressure has a significant positive correlation with the progression of intima-media thickness of carotid arteries (*26*) and with the occurrence of lacunar infarction (*27*) in the hypertensive population. It has also been reported that the SD value of daytime blood pressure is correlated with left ventricular mass index both in hypertensive patients (*28*) and in the general population (*29*). In addition, an increase in the SD value of blood pressure variability is associated with cognitive impairment (*30*). Furthermore, it has been shown that a

high SD value of daytime blood pressure is an independent predictor for cardiovascular mortality in the general population (*31*). In addition to these studies, the present study on elderly patients with hypertension showed that high values of blood pressure variability of both 24-h blood pressure and daytime blood pressure were independent predictors of cardiovascular events in those specific patients.

The mechanisms underlying the positive correlation between blood pressure variability and the incidence of cardiovascular events could not be addressed in this study. The blood pressure variability is influenced by baroreflex regulation. The afferent fibers of this reflex arise from the aortic arch and carotid artery bifurcations and, therefore, in patients with arteriosclerosis, the afferent signal of the baroreflex may be decreased owing to low compliance of the arteriosclerotic vascular wall (*32*). In the present study, there was no significant difference in baseline clinical background or mean blood pressure values between the high CV group and low CV group. However, there is a possibility that subclinical arteriosclerosis may have been more advanced in the high CV group, and that blood pressure variability was increased as a consequence. This might explain the finding that more cardiovascular events occurred in the high CV group. On the other hand, another possibility is that blood pressure variability could have a direct effect on clinical outcome. The acute hemodynamic change observed in the high CV group might be a trigger for acute catastrophic events. In addition, blood pressure variability itself could induce vascular and organ damage, which might subsequently lead to cardiovascular events. Indeed, it has been reported that structural alteration of arteries (*33*) and cardiac hypertrophy (*34*) are observed in an animal model of high blood pressure variability.

Our study has some limitations. We used the discontinuous method of measuring blood pressure. This method is indeed less invasive to the patients but did not permit their full range of activity, and thus did not allow the recording of their full potential range of variability compared with the invasive continuous method. Indeed, we measured blood pressure only every 30 min. Because this measurement represents a low frequency sampling, the accuracy of blood pressure variability estimates assessed by ABPM may be reduced (*35*). In addition, our pilot study showed statistically significant correlations in terms of the short-term reproducibility of parameters obtained with 24-h ABPM, but absolute values of the correlation coefficient were not high enough. Furthermore, the possibility cannot be excluded that patients with excess nocturnal fall of blood pressure (extreme dippers), a condition that has already been shown to be associated with cerebrovascular disease (*17*), may have been defined as high CV patients in the present study. Moreover, it has been reported that some antihypertensive drugs reduce blood pressure variability (*36*). Because all patients were treated with one or two antihypertensive drugs in this study, there is a possibility that patients with lower blood pressure variability may have received more effective treatment, leading to better cardiovascular outcomes, despite the fact that the average blood pressure levels were identical between the two groups. Patients with and without organ damage at baseline were mixed together for analysis. It is possible that the significance of blood pressure variability in patients with organ damage could be different from that in patients without organ damage, because the autoregulatory function in response to acute change in blood pressure might be impaired in patients with organ damage, and thus these patients might be more susceptible to cardiovascular events. To clarify this point, subgroup analysis with a larger number of patients is required.

The present study was performed retrospectively in a longitudinal fashion. We made only a single measurement of 24-h blood pressure for the prediction of further events. Therefore, a prospective study with larger sample size and with repeated measurement should be conducted in the future to confirm the findings obtained in this study.

In conclusion, our data indicate that blood pressure variability is an independent risk factor for cardiovascular events in elderly hypertensive patients. This finding suggests that not only the average blood pressure level but also blood pressure variability should be taken into consideration for the management of elderly hypertensive patients.

References

1. Kannel WB: Blood pressure as a cardiovascular risk factor. Prevention and treatment. *JAMA* 1996; **275**: 1571–1576.
2. National High Blood Pressure Education Program Working Group: National High Blood Pressure Education Program Working Group report on hypertension in the elderly. *Hypertension* 1994; **23**: 275–285.
3. Vogat TM, Ireland CC, Black D, Camel G, Hughes G: Recruitment of elderly volunteers for a multicenter clinical trial: the SHEP Pilot Study. *Control Clin Trials* 1986; **7**: 118–133.
4. Floras JS, Hassan MO, Jones JV, Osikowska BA, Sever PS, Sleight P: Factors influencing blood pressure and heart rate variability in hypertensive humans. *Hypertension* 1988; **11**: 273–281.
5. Convanico V, De Caprio L, Vigorito C, *et al*: Differences in blood pressure profile between young and elderly hypertensive patients. *J Hum Hypertens* 1990; **4**: 405–409.
6. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS: Orthostatic hypotension in older adults. The Cardiovascular Health Study. *Hypertension* 1992; **19**: 508–519.
7. Appelegate WB, Davis BR, Black HR, Smith WM, Miller ST, Burlando AJ: Prevalence of postural hypotension at baseline in the Systolic Hypertension in the Elderly Program (SHEP) cohort. *J Am Geriatr Soc* 1991; **39**: 1057–1064.
8. Jansen RWMM, Lipsitz LA: Postprandial hypotension: epidemiology, pathophysiology and clinical management. *Ann Intern Med* 1995; **122**: 286–295.
9. Shimada K, Kitazumi T, Sadakane N, Ogura H, Ozawa T: Age-related changes in baroreflex function, plasma norepinephrine and blood pressure. *Hypertension* 1985; **7**: 113–117.
10. Gribbin B, Pickering LTG, Slight P, Petro R: Effects of age

and high blood pressure on baroreflex sensitivity in man. *Circ Res* 1971; **29**: 424.
11. Drayer JIM, Weber MA, DeYoung JL, Wyle FA: Circadian blood pressure patterns in ambulatory hypertensive patients. Effects of age. *Am J Med* 1982; **73**: 493–499.
12. White WB, Lund-Johansen P, McCabe EJ: Clinical evaluation of the Colin ABPM 630 at rest and during exercise: an ambulatory blood pressure monitoring with gas-powered cuff inflation. *J Hypertens* 1989; **7**: 477–483.
13. SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**: 3255–3264.
14. Staessen JA, Fagard R, Thijis L, *et al*: Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350**: 757–764.
15. O'Brien E, Sheridan J, O'Malley K: Dippers and non-dippers. *Lancet* 1988; **ii**: 397.
16. Kario K, Shimada K: Change in diurnal blood pressure rhythm due to small lacunar infarct. *Lancet* 1994; **344**: 200.
17. Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K: Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. *Hypertension* 1996; **27**: 130–135.
18. Shimada K, Kawamoto A, Matsubayashi K, Nishinaga M, Kimura S, Ozawa T: Diurnal blood pressure variations and silent cerebrovascular damage in elderly patients with hypertension. *J Hypertens* 1992; **10**: 875–878.
19. Suzuki Y, Kuwajima I, Kanemaru A, *et al*: The cardiac function reserve in elderly hypertensive patients with abnormal diurnal change in blood pressure. *J Hypertens* 1992; **10**: 173–179.
20. Verdecchia P, Shillaci G, Guerrieri M, *et al*: Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 1990; **81**: 528–536.
21. Kikuya M, Sugimoto K, Katsuya T, *et al*: A/C1166 gene polymorphism of the angiotensin II type 1 receptor (AT1) and ambulatory blood pressure: the Ohasama Study. *Hypertens Res* 2003; **26**: 141–145.
22. Kario K, Schwartz JE, Gerin W, Robayo N, Maceo E, Pickering TG: Psychological and physical stress-induced cardiovascular reactivity and diurnal blood pressure variation in women with different work shifts. *Hypertens Res* 2002; **25**: 543–551.
23. Kario K, James GD, Marion R, Ahmed M, Pickering TG: The influence of work- and home-related stress on the levels and diurnal variation of ambulatory blood pressure and neurohumoral factors in employed women. *Hypertens Res* 2002; **25**: 499–506.
24. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G: Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertens* 1987; **5**: 93–98.
25. Frattola A, Parati G, Cuspidi C, Albini F, Mancia G: Prognostic value of 24-hour blood pressure variability. *J Hypertens* 1993; **11**: 1133–1137.
26. Sander D, Kukla C, Klingelhofer J, Winbeck K, Conrad B: Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis: a 3-year follow-up study. *Circulation* 2000; **102**: 1536–1541.
27. Kukla C, Sander D, Schwarze J, Wittich I, Klingelhofer J: Changes of circadian blood pressure patterns are associated with the occurence of lucunar infarction. *Arch Neurol* 1998; **55**: 683–688.
28. Veerman DP, de Blok K, van Montfrans A: Relationship of steady state and ambulatory blood pressure variability to left ventricular mass and urinary albumin excretion in essential hypertension. *Am J Hypertens* 1996; **9**: 455–460.
29. Sega R, Corrao G, Bombelli M, *et al*: Blood pressure variability and organ damage in a general population: results from the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). *Hypertension* 2002; **39**: 710–714.
30. Kanemaru A, Kanemaru K, Kuwajima I: The effects of short-term blood pressure variability and nighttime blood pressure levels on cognitive function. *Hypertens Res* 2001; **24**: 19–24.
31. Kikuya M, Hozawa A, Ohokubo T, *et al*: Prognostic significance of blood pressure and heart rate variabilities: the Ohasama study. *Hypertension* 2000; **36**: 901–906.
32. Appenzeller O, Descarries L: Circulatory reflexes in patients with cerebrovascular disease. *N Engl J Med* 1964; **271**: 820–823.
33. Sasaki S, Yoneda Y, Fujita H, *et al*: Association of blood pressure variability with induction of atherosclerosis in cholesterol-fed rats. *Am J Hypertens* 1994; **7**: 453–459.
34. van Vliet BN, Hu L, Scott T, Chafe L, Montani JP: Cardiac hypertrophy and telemetered blood pressure 6 wk after baroreceptor denervation in normotensive rats. *Am J Physiol* 1996; **271**: R1759–R1769.
35. Parati G, Saul JP, Di Rienzo M, Mancia G: Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. *Hypertension* 1995; **25**: 1276–1286.
36. Mancia G, Omboni S, Rovogli A, Parati G, Zanchetti A: Ambulatory blood pressure monitoring in the evaluation of antihypertensive treatment: additional information from a large data base. *Blood Press* 1995; **4**: 148–156.