Original Article

Morning Hypertension: The Strongest Independent Risk Factor for Stroke in Elderly Hypertensive Patients

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Stroke occurs most frequently in the morning hours, but the impact of the morning blood pressure (BP) level on stroke risk has not been fully investigated in hypertensives. We studied stroke prognosis in 519 older hypertensives in whom ambulatory BP monitoring was performed, and who were followed prospectively. During an average duration of 41 months (range: 1–68 months), 44 stroke events occurred. The morning systolic BP (SBP) was the strongest independent predictor for stroke events among clinic, 24-h, awake, sleep, evening, and pre-awake BPs, with a 10 mmHg increase in morning SBP corresponding to a relative risk (RR) of 1.44 ($p<0.0001$). The average of the morning and evening SBP (Av-ME-SBP; 10 mmHg increase: RR=1.41, $p=0.0001$), and the difference between the morning and evening SBP (Di-ME-SBP; 10 mmHg increase: RR=1.24, $p=0.0025$) were associated with stroke risks independently of each other. The RR of morning hypertension (Av-ME-SBP≥135 mmHg and Di-ME-SBP≥20 mmHg) *vs.* sustained hypertension (Av-ME-SBP≥135 mmHg and Di-ME-SBP<20 mmHg) for stoke events was 3.1 after controlling for other risk factors ($p=0.01$). In conclusion, morning hypertension is the strongest independent predictor for future clinical stroke events in elderly hypertensive patients, and morning and evening BPs should be monitored in the home as a first step in the treatment of hypertensive patients. (*Hypertens Res* 2006; 29: 581–587)

***Key Words*: morning hypertension, stroke, hypertension, elderly**

Introduction

Ambulatory blood pressure monitoring (ABPM) is now available for the clinical management of hypertensive patients, which enables the assessment of the relative importance of different parameters of blood pressure (BP) measured over 24 h. In addition, self-monitoring of home BP is now widely used in clinical practice for hypertensive patients (*1–3*). However, it remains unclear which BP-monitoring times (*e.g.*, morning *vs.* evening) are the most powerful predictors of stroke events.

There is a marked diurnal variation in the onset of cardiovascular events, with a peak incidence of myocardial infarction, sudden cardiac death, and ischemic and hemorrhagic stroke occurring in the morning (6 AM to noon) (*4–11*). In particular, 3-h after waking is the highest risk period of the day or night (*6*). BP shows a similar diurnal variation, reach-

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Table 1. Cox Regression Analysis for Clinical Stroke Events

Covariates	Model 1		Model 2	
	Relative risk (95% CI)	*p*-value	Relative risk (95% CI)	*p*-value
Clinic SBP (10 mmHg)	NS		—	
24-h SBP (10 mmHg)	NS		—	
Awake SBP (10 mmHg)	NS		—	
Evening SBP (10 mmHg)	NS		—	
Sleep SBP (10 mmHg)	NS		—	
Pre-awake SBP (10 mmHg)	NS		—	
Morning SBP (10 mmHg)	1.44 (1.25–1.67)	<0.0001	—	
Av-ME-SBP (10 mmHg)	—		1.41 (1.19–1.67)	0.0001
Di-ME-SBP (10 mmHg)	—		1.24 (1.08–1.42)	0.0025

After controlling for age, gender, body mass index, smoking status, diabetes, hyperlipidemia, silent cerebral infarct, and antihypertensive medication status at the final follow-up, all SBP variables (clinic, 24-h, awake, evening, sleep, pre-awake, and morning) were added in Model 1 and were analyzed by Stepwise Cox regression analysis, and both Av-ME-SBP and Di-ME-SBP were added in Model 2, and were analyzed by forced Cox regression analysis. CI, confidence interval; SBP, systolic blood pressure; Av-ME-SBP, average of the morning and evening SBP; Di-ME-SBP, difference between the morning and evening SBP; NS, not selected; —, not included in the model.

ing the highest level during the morning, and then declining to reach a trough value at about midnight (*10*). We recently demonstrated that morning BP surge has a substantial impact on stroke prognosis in elderly hypertensive patients (*12*). Thus, morning BP levels might be the best predictor of stroke risk in hypertensive patients.

In this study of elderly hypertensive patients, we studied the impact of morning BP on stroke prognosis in comparison with ambulatory blood pressure (ABP) parameters during other periods, in relation to silent cerebral infarct (SCI; a strong predictor of subsequent clinical stroke).

Methods

Subjects

This study employed 519 elderly hypertensive patients (mean age, 72 years) who were followed prospectively for an average of 41 months. This represented 98% of the 532 patients who were initially enrolled into the study from 6 participating institutes (3 clinics, 2 hospitals, and 1 outpatient clinic of a medical university) between January 1, 1992 and January 1, 1998. The subjects of this study were also examined in our previous study (*12*). They were selected from a larger cohort of hypertensive patients (Jichi Medical School ABPM Study) (*13*) by the following criteria: 1) essential hypertension with an average clinic systolic BP (SBP)≥140 mmHg and/or average clinic diastolic BP (DBP)≥90 mmHg (average for each patient on 2 or more occasions on different days); 2) age≥50 years; 3) a successful 24-h ABPM; and 4) the assessment of the presence or absence of SCI using brain MRI. No patient had taken any antihypertensive medication for at least 14 days before the ABPM study, but 55% had a prior history of antihypertensive medication use. We excluded from this study patients with renal failure (serum creatinine level>2.0 mg/dl), hepatic damage, obvious present illness, a past history of coronary artery disease, stroke (including transient ischemic attacks [TIA]), congestive heart failure, or arrhythmia. All of the subjects studied were ambulatory, and all gave informed consent for the study. The results of the ABPM and brain MRI were returned to the physicians who followed up the subjects. This study was approved by the regional Research Ethics Committee, Department of Cardiology, Jichi Medical School, Japan, in 1998.

Clinic BP was measured after resting for at least 5 min in the sitting position. Diabetes mellitus was defined by a fasting glucose level>140 mg/dl, a random non-fasting glucose level>200 mg/dl, hemoglobin A1c>6.2%, or the use of an oral hypoglycemic agent or insulin. Hyperlipidemia was defined by a total cholesterol level>240 mg/dl or the use of an oral lipid-lowering agent. Smokers were defined as current smokers. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

ABPM

Noninvasive ABPM was carried out on a weekday with one of three automatic devices (ABPM-630: Nippon Colin Co., Komaki, Japan; TM-2421 or TM-2425: A&D Co. Inc., Tokyo, Japan), which recorded BP and pulse rate every 30 min for 24 h. The accuracy of these devices was previously validated (*14*, *15*). The ambulatory data used in the present study were those obtained by the oscillometric method. We excluded those who obtained less than 80% of either awake or asleep valid BP readings ($n=31$). Patients who reported in our post-ABPM questionnaire that their sleep was severely dis-

turbed by wearing the ABPM were also excluded from this study (n=23).

BP values were defined as the average of 4 BP readings taken over one of the following 2-h periods: morning BP, the 2 h after waking up; evening BP, the 2 h before going to bed; and pre-awake BP, the 2 h before waking up. The morning–evening BP difference (Di-ME-BP) was defined as the morning BP minus the evening BP, and the morning–evening BP average (Av-ME-BP) as (morning BP plus evening BP)/2. Sleep BP was defined as the average of BPs from the time when the patient went to bed until the time he or she got out of bed, awake BP as the average of BPs recorded during the rest of the day, and 24-h BP as the average of BPs during a 24-h period. The lowest BP was defined as the average of the 3 lowest BP readings at nighttime.

Brain MRI

Brain MRI was performed using a superconducting magnet with a main strength of 1.5T (Toshiba MRT200FXII: Toshiba, Tokyo, Japan; SIGNA-Horizon, Ver. 5.8: General Electric Co., Milwaukee, USA; or Vision System: Siemens, Erlangen, Germany) within 3 months of the ABPM. T_1- and T_2-weighted images were obtained in the transverse plane with 7.8 mm- or 8.0 mm-thick sections. A SCI was defined as a low signal intensity area (3–15 mm) on T_1-weighted images that was also visible as a hyperintense lesion on T_2-weighted images, as described previously (*12*, *13*, *16*, *17*). Multiple SCI was defined as ≥2 infarcts. The MR images of the subjects were randomly stored and interpreted by investigators who were blind to the subjects' names and characteristics.

Follow-Up and Events

The patients' medical records were intermittently reviewed after ABPM, for the use of antihypertensive drug therapy and the occurrence of cardiovascular events. The follow-up was performed during a 20-month period from 1996 to 1998; the mean follow-up period was 41 months, with a range from 1 to 68 months. When patients failed to come to the clinic, we interviewed them by telephone. Stroke events were diagnosed by each physician who was caring for the patient at the time of the event. A stroke was diagnosed on the basis of a sudden onset of a neurological deficit persisting for >24 h in the absence of any other disease process explaining the symptom. Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and an undefined type of stroke. We excluded TIAs in which the neurological deficit cleared completely in <24 h from the onset of the symptoms.

Of the total of 532 eligible patients at baseline, a complete follow-up was performed in 519 (98%) patients, and the data analysis was restricted to these patients. Of these, 292 (56%) were on antihypertensive medication at the time of the final follow-up.

Statistical Analysis

Data are expressed as the mean±SD. Two-sided unpaired t-test and χ^2-test were used to test the differences between the 2 groups for the mean values of continuous measures and prevalence rates, respectively. Adjusted relative risks (RR) and 95% confidence intervals (CI) were calculated using Cox regression analysis. After controlling for age, gender, BMI, smoking status, diabetes, hyperlipidemia, silent cerebral infarct, and antihypertensive medication status at the final follow-up, all SBP variables (clinic, 24-h, awake, evening, sleep, pre-awake, and morning) were entered into Model 1 (Table 1) and were analyzed by Stepwise Cox regression analysis, and both Av-ME-SBP and Di-ME-SBP (the average of the morning and evening SBP and the difference between the morning and evening SBP, respectively) were entered into Model 2 (Table 1), and were analyzed by forced Cox regression analysis. The statistical calculations were performed using SPSS software, version 8.0J (SPSS Inc., Chicago, USA). Differences with $p<0.05$, two-tailed, were considered to be statistically significant.

Results

Morning BP Level *vs.* Other ABP Parameters

During an average duration of 41 months (range: 1–68 months), 44 stroke events (30 ischemic strokes, 6 hemorrhagic strokes, and 8 unknown subtype strokes), including 8 fatal strokes, occurred.

The morning SBP (10 mmHg increase: RR [95% CI]=1.44 [1.25–1.67], $p<0.0001$) was the strongest independent predictor for stroke events among the clinic, 24-h, awake, sleep, evening, and pre-awake SBPs (Model 1).

Morning BP Level *vs.* Morning BP Surge

We defined the morning BP surges (MBPS) using the previously reported formulas: 1) MBPS-1: Morning SBP minus the lowest sleep SBP; 2) MBPS-2: morning SBP minus the pre-awake SBP (*12*). After controlling for age, gender, BMI, smoking status, diabetes, hyperlipidemia, 24-h SBP, silent cerebral infarct, and antihypertensive medication status at the final follow-up, when the morning SBP and MBPS-1 were separately entered into the Cox regression model, both were significantly associated with stroke events (10 mmHg increase in morning SBP: RR [95% CI]=1.40 [1.14–1.72], $p=0.0012$; 10 mmHg increase in MBPS-1: RR [95% CI]=1.28 [1.10–1.48], $p=0.0011$). However, when both were entered into the same model, neither morning SBP (10 mmHg increase: RR [95% CI]=1.19 [0.79–1.80]) nor MBPS-1 (10 mmHg increase: RR [95% CI]=1.15 [0.85–1.54]) remained significant. MBPS-2 was also significantly associated with stroke risk events (10 mmHg increase: RR [95% CI]=1.17 [1.01–1.36], $p=0.039$). However, when both morning SBP

Table 2. Clinical and Blood Pressure Characteristics

	WCHT (n=147)	WCHT+Morning BP elevation (n=58)	Sustained HT (n=228)	Morning HT (n=86)	Total (n=519)
Age (years)	71±9.1	71±8.4	72±8.4	74±8.5	72±8.6
Male (%)	27	38	41†	42	37
Body mass index (kg/m^2)	23.9±3.7	23.8±3.2	24.4±3.5	24.1±3.8	24.1±3.6
Current smoker (%)	18	19	26	23	22
Hyperlipidemia (%)	24	26	22	15	22
Diabetes (%)	10	12	16	19	14
SBP (mmHg)					
Clinic	157±13	156±13	170±21*,‡	168±19*,‡	164±19
24-h	124±9.3	125±11	147±13*,‡	148±15*,‡	138±17
Awake	131±11	130±11	156±14*,‡	154±15*,‡	147±18
Evening	124±11	109±10*	153±15*,‡	138±15*,‡,§	137±21
Sleep	114±12	114±13	135±17*,‡	134±18*,‡	127±18
Pre-awake	120±13	123±15	142±19*,‡	146±22*,‡	134±21
Morning	124±11	138±10*	153±14*,‡	171±15*,‡,§	146±21
Av-ME	124±8.6	123±8.9	153±13*,‡	154±14*,‡	142±18
Di-ME	−0.35±13	30±11*	0.17±13‡	32±12*,§	8.6±19
DBP (mmHg)					
Clinic	85±13	85±12	96±14*,‡	94±14*,‡	91±14
24-h	71±5.9	72±8.4	83±8.6*,‡	83±9.3*,‡	79±9.9
Awake	74±7.1	73±7.5	87±9.2*,‡	87±9.7*,‡	82±11
Evening	71±7.7	63±7.4*	87±11*,‡	79±9.1*,‡,§	78±13
Sleep	66±6.7	65±7.8	77±10*,‡	76±11*,‡	72±11
Pre-awake	68±7.9	70±8.7	80±11*,‡	81±12*,‡	75±12
Morning	72±7.7	79±8.4*	87±10*,‡	94±12*,‡,§	83±13
Av-ME	72±6.4	71±6.4	87±9.1*,‡	86±9.4*,‡	81±11
Di-ME	0.56±8.6	16±9.4*	0.37±10‡	16±11*,§	4.7±12

Data are shown as the means±SD or percentages. BP, blood pressure; HT, hypertension; WCHT, white-coat hypertension; SBP, systolic BP; Av-ME, average of morning BP and evening BP; Di-ME, morning BP minus evening BP; DBP, diastolic BP. *p<0.001, †p<0.05, *vs*. WCHT group. ‡p<0.001 *vs*. WCHT+Morning BP elevation group. §p<0.001 *vs*. Sustained HT group.

Table 3. Silent Cerebrovascular Disease and Stroke Prognosis

	WCHT (n=147)	WCHT+Morning BP elevation (n=58)	Sustained HT (n=228)	Morning HT (n=86)	Total (n=519)
Baseline data (prevalence)					
Silent cerebral infarct (%)	41	34	58†,§	55	55
Multiple silent infarct[a] (%)	22	24	43*,‖	45*,‖	35
Prospective data					
Stroke incidence (%)	4.1	3.5	7.9	21*,‡,¶	8.5

Data are shown as percentages. BP, blood pressure; HT, hypertension; WCHT, white-coat hypertension. [a]≥2 silent cerebral infarcts per person. *p<0.001, †p<0.01, *vs*. WCHT group. ‡p<0.001, §p<0.01, ‖p<0.05, *vs*. WCHT+Morning BP elevation group. ¶p<0.001 *vs*. Sustained HT group.

and MBPS-2 were entered into the same model, only morning SBP remained significant (10 mmHg increase in morning SBP: RR [95% CI]=1.44 [1.07–1.94], p=0.016).

Definition of Morning Hypertension *vs*. Sustained Hypertension

As shown in Model 1, morning BP was the most important ABP parameter in predicting risk. We next attempted to define morning hypertension and sustained hypertension

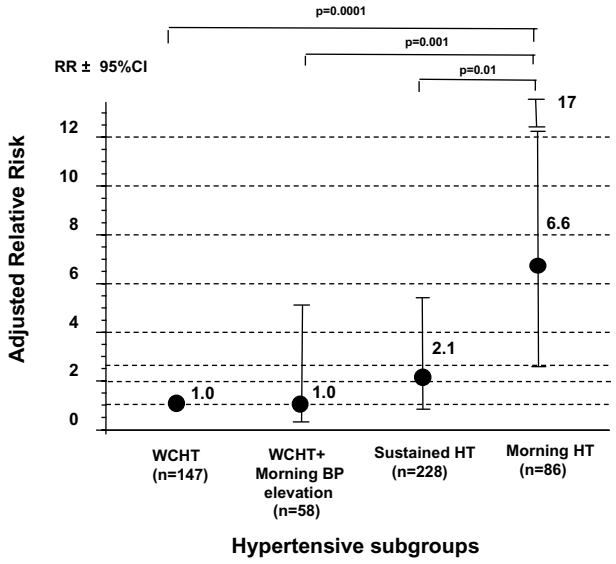

Fig. 1. *Relative risk (±1 SD range) of strokes after adjustment for age, gender, body mass index, smoking status, diabetes, hyperlipidemia, silent cerebral infarct, 24-h systolic blood pressure level, and antihypertensive medication status at the final follow-up*

using only morning BP and evening BP, both of which are readily measured by home BP monitoring. The mean±SD morning SBP and evening SBP for all the subjects were 146±21 mmHg and 137±21 mmHg, respectively. The study population included 134 patients (26%) with both morning SBP and evening SBP<135 mmHg, 29 (5.6%) with morning SBP<135 mmHg and evening SBP≥135 mmHg, 117 (23%) with morning SBP≥135 mmHg and evening SBP<135 mmHg, and 239 (46%) with both morning SBP and evening SBP≥135 mmHg.

The mean±SD Av-ME-SBP and Di-ME-SBP were 142±18 mmHg, and 86±29 mmHg, respectively. In Model 2 (Table 1), both the Di-ME-SBP (10 mmHg increase: RR [95% CI]=1.24 [1.08–1.42], $p=0.0025$) and the Av-ME-SBP (10 mmHg increase: RR [95% CI]=1.41 [1.19–1.67], $p=0.0001$) were associated with stroke risks independently of each other.

Since the cutoff value of the top quartile of Di-ME-SBP was 20.8 mmHg, we used a cutoff value of 20 mmHg for the definition of the high Di-ME-SBP group ($n=144$, 28% of total subjects). Using these classifications, we classified the subjects into 4 groups according to whether the hypertension was sustained (Av-ME-SBP>135 mmHg) or white-coat hypertension (WCHT group; Av-ME-SBP<135 mmHg), and whether there was a higher morning than evening SBP (Di-ME-SBP>20 mmHg), or not (Di-ME-SBP<20 mmHg). There were 147 patients (28%) in the WCHT group with no morning BP elevation, 58 (11%) in the WCHT group with morning BP elevation (WCHT+Morning BP elevation group), 228 (44%) in the group with sustained hypertension and no morning BP elevation (Sustained HT group), and 86 (17%) in the group with sustained hypertension and morning BP elevation (Morning HT group).

By definition, the Sustained HT and Morning HT groups had higher levels of clinic and ambulatory BP parameters than the WCHT groups (Table 2). However, there were no significant differences in the clinic BPs, Av-ME-BPs, 24-h BPs, awake BPs, or sleep BPs between the Sustained HT and Morning HT groups. The Di-ME-BPs were comparable between the WCHT+Morning BP elevation and Morning HT groups.

Silent and Clinical Cerebrovascular Disease in Morning Hypertension

The prevalence of SCI was significantly higher in the Sustained HT than in the WCHT and WCHT+Morning BP elevation groups, and tended to be higher in the Morning HT than in the WCHT+Morning BP elevation group ($p=0.08$). The prevalence of multiple SCI was higher in the Sustained HT and Morning HT groups than the WCHT and WCHT+Morning BP elevation groups (Table 3). However, there were no significant differences in the prevalence of SCI.

The stroke incidence was significantly higher in the Morning HT group than in the other 3 groups (all $p<0.001$) (Table 3). Figure 1 shows the RR (95% CI) of a stroke after adjusting for age, gender, BMI, smoking status, diabetes, hyperlipidemia, SCI, and antihypertensive medication status at the final follow-up. The stroke risk was significantly higher in the Morning HT group not only than in the WCHT groups but also than in the Sustained HT group (RR [95% CI]=3.1 [1.6–6.1], $p=0.01$), despite the fact that there were no differences in the clinic and 24-h BP levels.

Discussion

This study is the first to show that morning BP is the best predictor of subsequent stroke events in elderly hypertensive patients. The results of this study indicate that the most relevant period for hypertensive patients measuring their BP levels at home is in the morning. In addition, morning hypertension with an increase in both the Av-ME-BP and Di-ME-BP was a higher risk for stroke than sustained hypertension with similar increases of morning and evening BPs.

Morning BP Levels and Stroke Incidence

In these elderly hypertensive patients, the morning BP was unexpectedly more strongly associated with stroke risk than the 24-h BP. This suggests that some pathogenic mechanism related to morning BP is more closely associated with stroke risk than the total vascular BP overload throughout the 24-h period. In the morning, a number of conditions, such as platelet hyperactivity, impaired fibrinolytic activity, and increased

vasoconstriction, which are potential risk factors for triggering cardiovascular events, are aggregated (*4*, *8–11*, *18–24*), and when coupled with the increased shear stress on the atherosclerotic vascular wall resulting from the morning BP surge, might trigger stroke events.

Both morning BP level and morning BP surge in the Cox regression model were significantly associated with stroke risks. However, when both were entered into the same model, neither remained significant. This suggests that morning SBP and morning BP surge were equally important clinical predictors for strokes.

Morning BP and Evening BP

In this study, we attempted to predict strokes using morning BP and evening BP, which are commonly measured by home BP monitoring. The morning SBP level was comparable with awake SBP and was higher by 8.6 mmHg than the evening SBP in the total sample (Table 2). In the hypertensive patients defined using clinic BPs≥140/90 mmHg, when we used the cutoff SBP value of 135 mmHg, the prevalences of WCHT were 32% for morning SBP, 49% for evening SBP, and 39% for the Av-ME-SBP. Both the Av-ME-SBP and Di-ME-SBP were associated with future stroke events independently of each other.

Morning HT *vs.* Sustained HT

Since the Di-ME-SBP was a significant predictor of stroke even after classification of 2 groups by BP level (WCHT and true hypertension groups), we further subclassified the true hypertension group into the Morning HT group and Sustained HT group using the cutoff Di-ME-SBP of 20 mmHg (which almost corresponded to the top quartile). The Sustained HT group had the same high levels of morning and evening SBP (both 153 mmHg), while the Morning HT group had markedly higher morning SBP levels (171 mmHg) with only slightly increased evening SBP (138 mmHg). Although the Av-ME-SBP and -DBP, and the 24-h SBP and DBP were almost identical in the 2 groups, the stroke incidence was 2.7-times higher in the Morning HT group than the Sustained HT group. The RR of Morning HT group *vs*. Sustained HT group for stroke events was 3.1 after controlling for other risk factors and a baseline prevalence of SCI ($p=0.01$).

On the other hand, the stroke risk was comparable between the WCHT group without morning BP elevation and the WCHT group with morning BP elevation. Thus, the Di-ME-BP was clinically relevant only in the true hypertensive patients.

Clinical Stroke Events *vs.* Silent Cerebral Infarcts

The prevalence of SCI was comparable between the Morning HT and Sustained HT groups. Thus, the impact of morning BP might be different for the formation of SCI and the triggering of stroke events. SCI are usually small lacunar infarcts which occur in the small perforating cerebral arteries, in which sustained pressure overload might be more important for SCI formation. On the other hand, for the triggering of stroke events, which occur in cerebral vessels larger than those in which SCI occurs, mechanisms other than increased vascular overload might be involved. Platelets might be activated by increased shear stress acting on the atherosclerotic arterial wall during the morning period (*25*). Cerebral thrombosis formation due to platelet hyperactivity, and other thrombophilic properties that are augmented in the morning (*18–24*) might occur in relatively larger cerebral arteries to cause clinical stroke events.

Study Limitations

In this observational study, we did not collect any information about the BP-control status during the follow-up period. The impact of morning hypertension on the prognosis would be changed according to the medication status. Antihypertensive medications specifically targeted at morning BP would decrease the cardiovascular risk of morning hypertension.

Perspectives

In older hypertensive patients, a high morning BP was a stronger predictor of strokes than BP measured at other times of day. Since morning BP can easily be measured using home monitoring, these findings suggest that closer attention to its control might be beneficial for stroke prevention in hypertensive patients.

References

1. Nishinaga M, Takata J, Okumiya K, Matsubayashi K, Ozawa T, Doi Y: High morning home blood pressure is associated with a loss of functional independence in the community-dwelling elderly aged 75 years or older. *Hypertens Res* 2005; **28**: 657–663.
2. Ikeda T, Gomi T, Shibuya Y, *et al*: Morning rise in blood pressure is a predictor of left ventricular hypertrophy in treated hypertensive patients. *Hypertens Res* 2004; **27**: 939–946.
3. Kamoi K, Miyakoshi M, Soda S, Kaneko S, Nakagawa O: Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. *Diabetes Care* 2002; **25**: 2218–2223.
4. Muller JE, Tofler GH, Stone PH: Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation* 1989; **79**: 733–743.
5. Marler JR, Price TR, Clark GL, *et al*: Morning increase in onset of ischemic stroke. *Stroke* 1989; **20**: 473–476.
6. Willich SN, Goldberg RJ, Maclure M, Perriello L, Muller JE: Increased onset of sudden cardiac death in the first three hours after awakening. *Am J Cardiol* 1992; **70**: 65–68.
7. Mittleman MA, Maclure M, Tofler GH, *et al*: Triggering of acute myocardial infarction by heavy physical

exertion—protection against triggering by regular exertion. *N Engl J Med* 1993; **329**: 1677–1683.
8. Muller JE, Abela GS, Nesto RW, Tofler GH: Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. *J Am Coll Cardiol* 1994; **23**: 809–813.
9. Muller JE: Circadian variation in cardiovascular events. *Am J Hypertens* 1999; **12**: 35S–42S.
10. White WB: Cardiovascular risk and therapeutic intervention for the early morning surge in blood pressure and heart rate. *Blood Press Monit* 2001; **6**: 63–72.
11. Shimada K, Kario K, Umeda Y, Hoshide S, Hoshide Y, Eguchi K: Early morning surge in blood pressure. *Blood Press Monit* 2001; **6**: 349–353.
12. Kario K, Pickering TG, Umeda Y, *et al*: Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 2003; **107**: 1401–1406.
13. Kario K, Shimada K, Schwartz JE, Matsuo T, Hoshide S, Pickering TG: Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. *J Am Coll Cardiol* 2001; **38**: 238–245.
14. White WB, Lund-Johansen P, McCabe EJ: Clinical evaluation of the Colin ABPM 630 at rest and during exercise: an ambulatory blood pressure monitor with gas-powered cuff inflation. *J Hypertens* 1989; **7**: 477–483.
15. Imai Y, Sasaki S, Minami N, *et al*: The accuracy and performance of the A&D TM 2421, a new ambulatory blood pressure monitoring device based on the cuff-oscillometric method and the Korotkoff sound technique. *Am J Hypertens* 1992; **5**: 719–726.
16. 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.
17. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K: Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001; **38**: 852–857.
18. Rosing DR, Brakman P, Redwood DR, *et al*: Blood fibrinolytic activity in man. Diurnal variation and the response to varying intensities of exercise. *Circ Res* 1970; **27**: 171–184.
19. Ehrly AM, Jung G: Circadian rhythm of human blood viscosity. *Biorheology* 1973; **10**: 577–583.
20. Decousus HA, Croze M, Levi FA, *et al*: Circadian changes in anticoagulant effect of heparin infused at a constant rate. *Br Med J* (*Clin Res Ed*) 1985; **290**: 341–344.
21. Tofler GH, Brezinski D, Schafer AI, *et al*: Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. *N Engl J Med* 1987; **316**: 1514–1518.
22. Ridker PM, Manson JE, Buring JE, Muller JE, Hennekens CH: Circadian variation of acute myocardial infarction and the effect of low-dose aspirin in a randomized trial of physicians. *Circulation* 1990; **82**: 897–902.
23. Bridges AB, Scott NA, McNeill GP, Pringle TH, Belch JJ: Circadian variation of white blood cell aggregation and free radical indices in men with ischaemic heart disease. *Eur Heart J* 1992; **13**: 1632–1636.
24. Muller JE, Kaufmann PG, Luepker RV, Weisfeldt ML, Deedwania PC, Willerson JT: Mechanisms precipitating acute cardiac events: review and recommendations of an NHLBI workshop. *Circulation* 1997; **96**: 3233–3239.
25. Goto S, Ikeda Y, Saldivar E, Ruggeri ZM: Distinct mechanisms of platelet aggregation as a consequence of different shearing flow conditions. *J Clin Invest* 1998; **101**: 479–486.