発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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AJH 2005; 18:149–151

Editorial

Time for Focus on Morning Hypertension: Pitfall of Current Antihypertensive Medication

Kazuomi Kario

It is well-known that cardiovascular events occur more frequently in the morning.[1] The ambulatory blood pressure (BP) level also increases during the period from night to early morning, and changes with various psychologic and physical stress conditions.[2–4] Moreover, in the early morning, other cardiovascular risks such as thrombophilic tendencies and endothelial dysfunction are potentiated. Thus, the effect of high BP on cardiovascular risk is greater in the morning than during the other periods of the day. Theoretically, there are two types of morning hypertension (Fig. 1). The nondipper/riser (nocturnal hypertension) type, with persistent high BP from night-time to morning, is well-known to be associated with risk for damage to all target organs (brain, heart, and kidneys) and cardiovascular events.[5] The other type, the morning BP surge type, is associated in part with the extreme-dipping status of nocturnal BP, which we have previously reported to be associated with stroke risk.[6]

Morning BP surge is one of the components of diurnal BP variation, and it could be considered to be the ambulatory BP variability during "morning" stress.[7] Excessive morning BP surge seems to be an independent risk for cardiovascular disease, particularly in older hypertensives with impaired autoregulation of hypertensive target organs. There have been two relatively small prospective studies supporting the possible risk of morning BP surge. One was our Jichi Medical School ABPM Study (Wave 1) on 519 older hypertensive patients,[8] in which we conducted 24-h ambulatory BP monitoring at baseline, and prospectively studied the prognosis for stroke during the follow-up period of 41 months. We defined the morning BP surge as the morning BP (the average of 2 h after arising) minus the night-time lowest BP (the average of the three BP). Because moderate morning BP surge is a physiologic phenomenon, we consider that excessive morning BP surge is a risk for cardiovascular disease. We classified the hypertensive patients studied into a morning surge group and a nonsurge group, using a cutoff value of 55 mm Hg (top 10th percentile of morning surge in systolic BP). When we identified one or more nonsurge subjects who could be matched for age and 24-h systolic BP level to one morning surge subject, and weighted the controls to simulate a balanced design, clinical stroke events occurred more frequently during the follow-up period in the morning surge group than in the nonsurge group. In this study, silent cerebral infarcts detected by brain magnetic resonance imaging were more common in the former group. In our recent study,[9] multiple silent cerebral infarcts in the older hypertensives were significantly associated with α-adrenergic morning BP surge (defined by the reduction of the morning BP surge by an α-blocker).

Another recent French prospective study on 507 hypertensive patients also found results similar to ours.[10] They used the waking BP surge, defined as the morning systolic BP measured in a standing position minus the systolic BP before rising, and divided the hypertensive patients into quartiles of waking surge. Although there were no significant differences in the 24-h BP levels among each group, left ventricular hypertrophy assessed by echocardiography at baseline was more advanced and cardiovascular complications during the follow-up period occurred more frequently in the higher quartile groups. In the multivariate analysis, waking morning BP surge was significantly associated with cardiovascular risk independently of age and 24-h BP level.

In a recent unique study in which ABPM was conducted for 7 days in a community-dwelling population, Murakami et al[11] found significant variation of morning BP and daytime BP during the week, whereas there was no significant difference in the night-time BP among the days of the week. Morning BP level and morning BP surge were highest on Monday, compared to those on the other days of the week. This "Monday morning surge" may contribute to cardiovascular risk, which is highest on Monday. It is well-known that cardiovascular events occur most frequently on Monday.[12]

There has been no conclusive study on the associa-

Received August 30, 2004. First decision September 4, 2004. Accepted September 8, 2004.

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.09.007

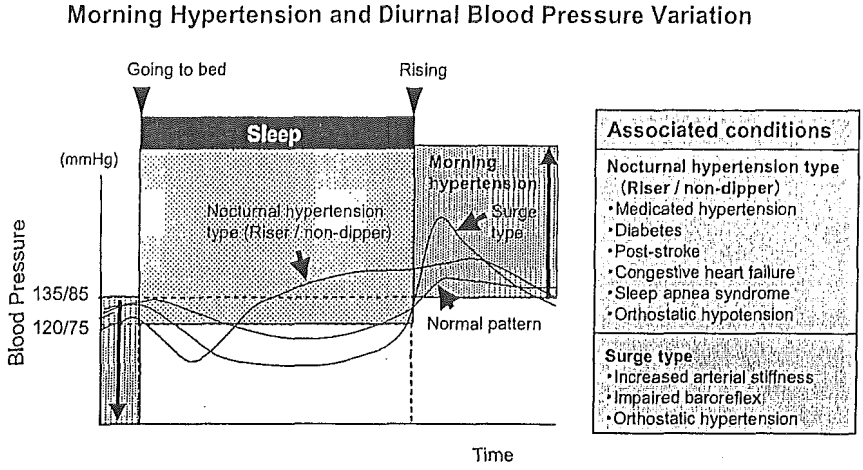

FIG. 1 Morning hypertension and diurnal blood pressure variation.

tion between diurnal BP variation and the onset time of cardiovascular events. However, the morning BP surge group had a higher incidence of stroke events in the morning than the nonsurge group, in our study on elderly hypertensive patients.[8] In addition, there is a possibility that diurnal variation of onset time of cardiovascular events may be nonexistent in nondippers. In depressive patients, nocturnal onset of acute myocardial infarction is significantly more common,[13] and diabetic patients exhibited less significant diurnal variation of onset time of acute myocardial infarction.[14] Subclinical depression, a newly recognized cardiovascular risk factor, is associated with poor sleep quality. In our recent study, we found that depression in men is associated with a disrupted diurnal BP variation (a tendency to the nondipping pattern) that is independent of changes in physical activity.[15]

Once-daily antihypertensive drugs are now widely used, however, in medicated hypertensives, even those whose clinic BP is well-controlled; the morning BP level before taking medicine is frequently high.[16] Therefore, morning hypertension is the blind spot in the current clinical practice for hypertension. Self-measured home BP monitoring and more specific management targeting morning hypertension[17–20] will achieve a more beneficial cardiovascular outcome in hypertensive patients.

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Morning Surge and Variability in Blood Pressure
A New Therapeutic Target?

Kazuomi Kario

Ambulatory blood pressure (BP) exhibits significant diurnal variation with modification of various psychological and physical stimulations during daily living.[1] There is a consensus that the average ambulatory BP levels over 24 hours are more closely associated with hypertensive target organ damage and cardiovascular event than clinical BP.[2] In addition, exaggerated ambulatory BP variation may be important in addition to the average BP level. However, results of previous studies that attempted to demonstrate the association between BP variability and cardiovascular disease are inconsistent. Some studies have found that ambulatory BP variability is a significant and independent determinant of target organ damage and poor cardiovascular prognosis,[3,4] whereas others have not found an independent association.[5] The reason for these inconsistent results is partly the modification of diurnal BP variation. Abnormal diurnal BP variation, such as marked nocturnal BP falls (extreme dippers) or the exaggerated morning BP surge, and reverse diurnal BP variation patterns with higher sleep BP than awake BP (risers) are risks for target organ damage and cardiovascular events.[6–8] These phenotypes of ambulatory BP variability are associated partly with each other and with 24-hour ambulatory BP variability. Abnormal diurnal BP variability is associated with other relatively shorter BP variability, such as orthostatic BP variabilities in elderly hypertensives.

In this issue, Zakopoulos et al newly introduce time rate of BP variation,[9] which is a measure of speed of BP variation, to evaluate the effect of BP variability components on target organ damage. They found the steeper BP variability, which is greater in hypertensives than in normotensives, is closely associated with increased carotid artery intima-media thickness (CA-IMT) independently of ambulatory BP level, the magnitude of BP variability, and nocturnal BP dipping. This indicates that a steeper rate of BP variability, which more closely triggers exaggerated shear stress and wall tension, is a potential independent cardiovascular risk in hypertensive patients. Interestingly, they found that a greater rate of BP variability during the morning BP surge (6:00 AM to 10:00 AM) was also associated with increased CA-IMT, independently of the morning BP level. Because baroreceptor sensitivity reduces in the morning, the impact of BP variability and its rate may be more markedly enhanced in the morning than in other periods. The increased morning surge and rate of variability in BP may partly explain the fact that cardiovascular events occur more frequently in the morning. In fact, there are 2 prospective studies to support the possible risk of exaggerated morning BP surge and cardiovascular events independently of 24-hour BP level in hypertensive patients.[6,10]

Various mechanisms may be involved in the association between BP variability and cardiovascular disease, and the impact of this association may be augmented in the morning. Experimentally, increased BP variability impairs endothelial function by inhibiting NO production and enhances neointimal formation after balloon injury, and may thereby contribute to atherogenesis.[11] Neurohumoral activation, which is increased in those with increased BP variability, may also increase the risk of cardiovascular disease. Increased sympathetic activity, particularly the α-adrenergic component, increases vascular tone in the resistance arteries and may contribute to the morning BP surge. In addition, coronary spasms are more likely to occur in the morning. One mechanism by which the morning BP surge may trigger vascular spasm is by increased shear stress on the vascular wall. An increase in plasma cortisol levels could enhance coronary artery sensitivity to the vasoconstrictor effects of catecholamines. In particular, morning BP surge associated with α-adrenergic activity is closely associated with multiple silent cerebral infarcts in older hypertensive patients.[7] The renin-angiotensin-aldosterone system (RAAS) is also activated in the morning and could contribute to morning BP surge and morning increase in cardiovascular risk. It was demonstrated recently that in addition to circulating factors in the cardiovascular system, the tissue RAAS also exhibits diurnal variation, possibly in relation to a clock gene.[12] In addition to systemic RAAS, morning activation of the tissue RAAS could be suppressed effectively, leading to increased protection against hypertensive target organ damage and cardiovascular events in hypertensive patients.

In addition to augmented mechanical stress on the cardiovascular system (which leads to cardiovascular remodeling), increased variability of blood flow by augmented BP variability increases shear stress on endothelial cells advancing atherosclerosis. Even in healthy subjects, flow-mediated dilatation of the brachial artery was diminished in the early morning when compared with the other periods (later in the morning and in the evening), whereas nonflow-mediated dilatation was comparable in the morning and in the other

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The opinions expressed in this editorial commentary are not necessarily those of the editors or of the American Heart Association.

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(*Hypertension*. 2005;45:485-486.)

Hypertension is available at http://www.hypertensionaha.org
DOI: 10.1161/01.HYP.0000158313.57142.3f

periods. The degree of morning endothelial cell dysfunction found in healthy subjects was similar to that found in high-risk patients with cardiovascular risk factors, such as diabetes and hyperlipidemia.

Other contributory changes are thrombophilic tendencies including increased platelet aggregation and an increase in levels of hematocrit and fibrinogen, which leads to increased blood viscosity. Potentiation of these factors is partly triggered by getting out of bed in the morning. Platelets could be activated by high shear stress occurring at stenotic areas of atherosclerotic arteries, morning BP surge per se could trigger increased platelet aggregation in the morning. Plasminogen activator inhibitor-1 (PAI-1), which inhibits tissue-type plasminogen activator leading to impaired fibrinolysis, also shows a morning increase. A clock gene has been identified recently in peripheral tissues, as well as in the central suprachiasmatic nucleus of the brain. PAI-1 production levels are partly regulated by a peripheral clock gene and partly by components of the RAAS system, shown by the infusion of angiotensin II causing an increase in PAI-1 levels. Further experimental studies are necessary to study the synergic effect of BP variability in the morning on hypertensive target organ damage in relation to neurohumoral and cardiovascular risk factors partly regulated by central and peripheral clock genes.

In international guidelines of hypertension management, cardiovascular risk stratification depends on the BP level and the status of the target organ damage. In addition to these 2 major predictors, BP variability may be the possible third axis of risk stratification. Further prospective and interventional studies are necessary to establish the clinical impact of BP variation, particularly in the morning, on target organ damage and cardiovascular events in hypertensive patients. Clinically, in addition to conventional hypertension management, the specific antihypertensive treatment targeting morning hypertension and exaggerated morning BP surge may achieve more beneficial target organ protection and prevention of cardiovascular events.

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AJH 2004; 17:668-675

Morning Blood Pressure Surge and Hypertensive Cerebrovascular Disease

Role of the Alpha Adrenergic Sympathetic Nervous System

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Background: The morning surge of blood pressure (BP) is associated with α-adrenergic activity. We studied the association between the α-adrenergic morning surge in BP and silent cerebrovascular disease in elderly patients with hypertension.

Methods: We conducted ambulatory BP monitoring three times (twice at baseline and after nighttime dosing of the α_1-blocker doxazosin) in 98 elderly hypertensive patients in whom the presence of silent cerebral infarcts (SCI) was assessed by brain magnetic resonance imaging. The morning BP surge (MBPS) was calculated as the mean systolic BP during the 2 h after waking minus the mean systolic BP during 1 h that included the lowest sleep BP. The α-adrenergic MBPS was calculated as the reduction of MBPS by doxazosin.

Results: The prevalence of multiple SCI was higher in the Surge group (top quartile: MBPS ≥45 mm Hg, n = 24) than in the Nonsurge group (MBPS <45 mm Hg, n = 74) (54% *v* 31%, P = .04), and in the higher α-adrenergic surge group (top quartile: α-adrenergic MBPS ≥28 mm Hg, n = 25) than in the lower α-adrenergic surge group (<28 mm Hg, n = 73) (68% *v* 26%, P < .0001). In the Surge group, subjects with higher α-adrenergic surge (n = 17) had a markedly higher frequency of multiple SCI, whereas none in the lower α-adrenergic surge group had multiple SCI (n = 7) (77% *v* 0%, P = .001). The α-adrenergic MBPS was closely associated with multiple SCI (10 mm Hg increase: OR = 1.96, P = .006), independently of age, MBPS, 24-h systolic BP, and other confounding factors.

Conclusion: The morning BP surge, particularly that dependent on α-adrenergic activity, is closely associated with advanced silent hypertensive cerebrovascular disease in elderly individuals. Am J Hypertens 2004;17: 668–675 © 2004 American Journal of Hypertension, Ltd.

Key Words: Hypertension, elderly, morning surge, sympathetic activity, cerebrovascular disease.

Cardiovascular events occur more commonly in the morning than at other times of day, and the diurnal blood pressure (BP) variation also shows a peak early in the morning.[1,2] We have recently clarified that the morning BP surge is risk for stroke events independently of 24-h BP level in elderly individuals with hypertension.[3] It is generally accepted that the sympathetic nervous system plays a major role in the regulation of BP changes, and therefore an increase in α-adrenergic activity might be one of the major determinants of this morning BP surge.[4] In fact, the Hypertension and Lipid Trial (HALT) study disclosed that the BP reduction with an α-blocker, doxazosin, was most pronounced in the morning period.[5,6] Furthermore, it is also possible that the morning increase in α-adrenergic activity and related BP surge contribute to the morning peak of cardiovascular events.

There is some evidence indicating that aging is associated with increased sympathetic nervous activity[7] and that central nervous system mechanisms mediate this process.[8] This systemic increase in sympathetic activity in older subjects might be expected to cause or to exacerbate hypertension and cardiac and vascular hypertrophy.[9,10] Autonomic dysfunction, which is mainly related to increased sympathetic activity, is frequently present in pa-

Received December 23, 2003. First decision February 21, 2004. Accepted April 6, 2004.

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This study was supported by grants-in-aid (1992–2001) from the Foundation for the Development of the Community (KK), Tochigi, Japan, and by a grant (HL57450) from the United States National Heart, Lung, and Blood Institute (TGP).

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0895-7061/04/$30.00
doi:10.1016/j.amjhyper.2004.04.001

tients with clinical cerebrovascular disease.[11,12] In elderly persons with hypertension, silent cerebral infarcts (SCI) are commonly found and are one of the strongest predictors of strokes.[13] However, the associations between the morning increase in α-adrenergic activity and the related BP surge with silent hypertensive target organ damage have not been thoroughly investigated.

To study the association between the morning BP surge (particularly the component associated with α-adrenergic activity) and silent cerebrovascular disease, we investigated the effect of nighttime dosing of doxazosin on the morning BP surge using ambulatory BP monitoring (ABPM) in asymptomatic elderly hypertensive individuals, with or without SCI detected by brain magnetic resonance imaging (MRI).

Methods

Patient Selection

This was an open-label study of the effects of doxazosin on ambulatory BP, which included older Japanese hypertensive patients at three Japanese hospital clinics. The entry period was June 1996 to January 2001. A total of 106 patients who were either untreated or were off medication for at least 1 week at the time of entry were studied. The entry BP criterion was ≥140 mm Hg for an average of a seated clinic systolic BP (SBP) or ≥90 mm Hg for diastolic BP (DBP) during the follow-up period (3 to 5 weeks). To be included in the study, patients had to be ≥60 years of age, to have a diagnosis of essential hypertension, and to have no history of other significant medical disorders including diabetes or any clinically overt cardiovascular disease. All participants were fully ambulant.

Body mass index was calculated as weight (kg)/height $(m)^2$. Electrocardiographically verified left ventricular hypertrophy was defined by abnormally high voltages of QRS complexes (R in V5 plus S in V1 >3.5 mV) associated either with flat T waves (<10% of R) or with ST segment depression and biphasic T waves.

Study Design

Each patient was studied for a maximum of 11 weeks, with an observation period of 3 to 5 weeks, a titration period of up to 4 weeks, and 1 to 5 weeks of maintenance therapy. After the observation period, patients were started on 1 mg doxazosin daily, taken at bedtime. The dose was doubled at weekly intervals until the average seated BP had fallen 1) by at least 20/10 mm Hg from the baseline level, or 2) by at least 10/5 mm Hg from the baseline level when baseline BP was <160/90 mm Hg. If BP reduction reached the above criteria at each of two consecutive visits, if a maximal daily dose of 8 mg doxazosin had been reached, or if adverse effects had occurred, no further dose increase was attempted. After the titration phase there was a maintenance phase of 1 to 5 weeks on the same dose of doxazosin. This protocol was modified from that of the HALT study.[5,6] Informed consent was obtained from all subjects, and the study was approved by the Research Ethical Committee of Department of Cardiology, Jichi Medical School.

We excluded three patients for whom at least one of the three BP recordings was not evaluable because of the presence of artifacts in >20% of either awake or asleep measurements. One patient who refused a second ABPM and two patients who reported that their sleep was severely disturbed by the ABPM were also excluded from the analysis. Two patients who developed orthostatic dizziness (one during the observation period and one during the titration period) were also discontinued from the study. Accordingly, three complete sets of ABPM data were successfully obtained in 98 patients.

Ambulatory BP Monitoring

Noninvasive ABPM was carried out three times on a weekday with one of two automatic ABPM devices (TM-2421 or TM-2425; A&D Co. Inc., Tokyo, Japan), which recorded BP and pulse rate by the oscillometric method every 30 min for 24 h. The accuracy of these devices was previously validated. The first ABPM was performed at the time of entry after being unmedicated for at least 2 weeks, the second ABPM at the end of the drug-free baseline period (3 to 5 weeks), and the third at the end of the maintenance period (1 to 5 weeks). The interval between the first and second ABPM and between the second and third ABPM were 3 to 5 weeks and 4 to 6 weeks, respectively.

We defined 24-h BP as the average of all BP readings throughout 24 h. All subjects were ambulant during the day, and none reported staying in bed after waking. Sleep BP was defined as the average of BP from the time when patients went to bed until the time they got out of bed, and awake BP as the average of BP recorded during the rest of the day. Morning BP was defined as the average of BP during the first 2 h after waking (four BP readings). The lowest BP was defined as the average BP of three readings centered on the lowest nighttime reading (that is, the lowest reading plus the readings immediately before and after). Evening BP was defined as the average BP during the 2 h before going to bed (four BP readings). Preawake BP was defined as the average BP during the 2 h just before waking (four BP readings). The morning BP surge (MBPS) was calculated as the morning SBP minus the lowest SBP. Systolic pressures were used for all of these calculations. We subclassified the patients according to the extent of the MBPS as follows: the top quartile of MBPS (≥45 mm Hg, $n = 24$, the Surge group), versus all others ($n = 74$, the Nonsurge group). The α-adrenergic MBPS was calculated as the baseline MBPS (the average of the first and second MBPS) minus the third MBPS (during doxazosin therapy).

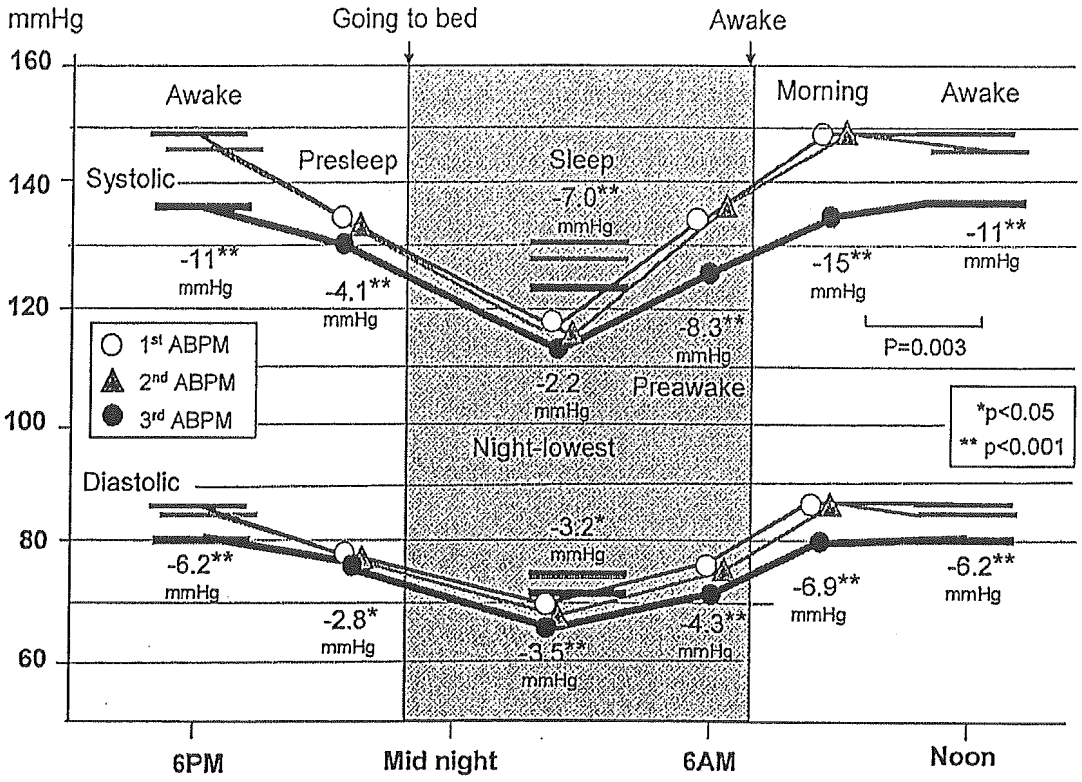

FIG. 1. Ambulatory blood pressure (BP) values during the two baseline recordings and after doxazosin therapy.

Brain MRI

Brain MRI was performed using a superconducting magnet with a main strength of 1.5 T (Toshiba MRT200FXII, Toshiba, Tokyo, Japan; SIGNA-Horizon version 5.8, General Electric Co.; or Vision, Siemens, Munich, Germany) during the period of ≤3 months before the first ABPM and the initiation of doxazosin treatment after the second ABPM. T1- and T2-weighted images were obtained in the transverse plane with sections 7.8 mm or 8.0 mm thick. An SCI was defined as a low signal intensity area (3 to 15 mm) on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images, as previously described.[13–15] Multiple SCI was defined as two or more infarcts. All SCI detected were lacunar infarcts of <15 mm. The MRI images of the subjects were randomly stored and interpreted by a professional blind to the subjects' names and characteristics. The κ statistics assessing inter-reader and intrareader agreement (non-SCI, one SCI, and multiple SCI) were 0.70 and 0.80, respectively, in our laboratory.

Statistical Analysis

The analysis was conducted using data from the 98 patients in whom brain MRI and three ambulatory BP recordings were successfully obtained. The changes from the baseline values were analyzed statistically using paired t tests for each subgroup. Two-sided unpaired t tests and χ^2 tests were used to test differences between the two groups in the mean values of continuous measures and prevalence rates, respectively. One-way analysis of covariance (ANCOVA) (controlling for age, sex, body mass index, smoking status, hyperlipidemia, duration of hypertension, dose of doxazosin, and 24-h systolic BP) were performed to detect differences among groups. Spearman correlation coefficients were calculated. Adjusted odds ratios (OR) and 95% confidence intervals (CI) of the presence of multiple SCI (two or more per person) versus single SCI or no SCI per person was calculated using multiple logistic regression analysis (multiple SCI = 1, one or no SCI = 0). Multiple linear regression analysis was used to test the differences in the slope of the relationship of MBPS and α-adrenergic MBPS between patients with and without multiple SCI. The criterion for determining statistical significance was $P < .05$. Results are given as mean ± SD.

Results

Ambulatory BP

Figure 1 shows the ambulatory BP values during the two baseline recordings and after doxazosin therapy. Nighttime dosing of doxazosin reduced morning BP more effectively than the other ambulatory BP parameters. There was no significant effect of doxazosin on the lowest SBP at night.

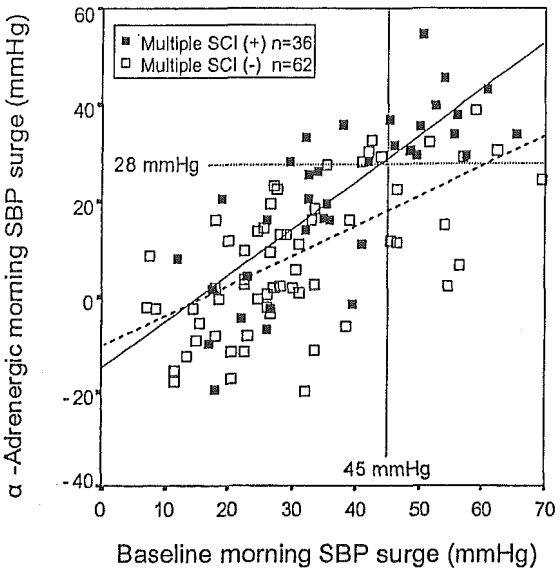

FIG. 2. Baseline morning blood pressure (BP) surge and the BP response to doxazosin. SBP = systolic BP; SCI = silent cerebral infarct.

Morning BP Surge

At baseline, the average MBPS was 33 ± 16 mm Hg for SBP and 17 ± 8.3 mm Hg for SBP (the average of the first and the second ABPM data), and the correlation coefficients between MBPS calculated from the first ABPM and the second ABPM were 0.66 for SBP and 0.42 for DBP (both $P < .0001$). The α-adrenergic MBPS (reduction of MBPS by doxazosin) was 13 ± 17 mm Hg for SBP and 3.4 ± 12 mm Hg for DBP. The α-adrenergic MBPS was significantly correlated with the baseline MBPS ($r = 0.73$, $P < .001$; Fig. 2).

The Surge group had significantly higher prevalences of left ventricular hypertrophy, multiple SCI, and number of SCI than the Nonsurge group (all $P < .05$), whereas the age and clinic and 24-h BP levels were comparable between the two groups (Table 1). Even after adjusting for possible confounding factors (age, sex, body mass index, smoking status, hyperlipidemia, duration of hypertension, dose of doxazosin, and 24-h systolic BP), the higher prevalence of multiple SCI in the Surge group remained significant ($P \leq .05$; Table 2). Both the MBPS ($P < .05$) and α-adrenergic MBPS ($P < .001$) were significantly associated with the number of SCI (Table 3). The α-adrenergic MBPS was significantly associated with smoking ($P < .01$) but with not with age or body mass index.

Silent Cerebral Infarction

The prevalence of multiple SCI was higher in the Surge group (top quartile: MBPS ≥ 45 mm Hg, $n = 24$) than in the Nonsurge group (MBPS < 45 mm Hg, $n = 74$) (54% *v* 31%, $P = .04$). Those with the highest α-adrenergic MBPS (top quartile: α-adrenergic MBPS ≥28 mm Hg, $n = 25$) had a higher prevalence of SCI (68% *v* 34%, $P = .005$) and multiple SCI (68% *v* 26%, $P < .0001$) than those with a lower α-adrenergic MBPS (α-adrenergic MBPS

Table 1. Clinical and blood pressure (BP) characteristics

Measure	Total Group ($n = 98$)	Surge Group* ($n = 24$)	Nonsurge Group* ($n = 74$)
Age (y)	70 ± 6.8	70 ± 6.7	70 ± 6.9
Male (%)	44	43	44
Body mass index (kg/m^2)	23.5 ± 3.2	23.8 ± 2.8	23.2 ± 3.3
Current smoker (%)	39	43	37
Hyperlipidemia (%)	33	43	29
Duration of hypertension (y)	6.0 ± 7.0	7.8 ± 8.1	5.4 ± 6.6
Left ventricular hypertrophy (%)	16	30§	12
Dose of doxazosin (mg/day)	3.7 ± 1.9	3.5 ± 1.8	3.7 ± 1.9
Clinic systolic BP (mm Hg)†	158 ± 9.9	160 ± 11	158 ± 9.7
Clinic diastolic BP (mm Hg)†	87 ± 10	89 ± 10	86 ± 10
24-h systolic BP (mm Hg)†	142 ± 12	142 ± 8.4	141 ± 13
24-h diastolic BP (mm Hg)†	82 ± 8.0	83 ± 6.0	82 ± 8.5
Silent cerebral infarct			
Prevalence (%)	43	57	39
Average number/person	1.5 ± 2.2	2.4 ± 2.4§	1.3 ± 2.1
Multiple silent cerebral infarct‡ prevalence (%)	37	57§	31

Data shown as mean ± SD or percentages.

* Morning BP Surge (morning BP [average of 2-h systolic BP after waking] minus lowest BP during sleep [nighttime three consecutive BP including lowest systolic BP] using average of first and second ambulatory BP) ≥45 mm Hg for Surge group and <45 mm Hg for Nonsurge group.

† Average of first and second ambulatory BP.

‡ Two or more silent infarcts.

§ $P < .05$, *v* Nonsurge group.

Table 2. Adjusted silent cerebral infarct status between morning blood pressure surge and nonsurge groups

Measure	Surge Group (n = 24)	Nonsurge Group (n = 74)	P
Silent cerebral infarct			
Prevalence (%)	55	39	.184
Average number/person	2.2 ± 0.42	1.3 ± 0.24	.086
Multiple silent cerebral infarct prevalence (%)	53	31	.045

Data shown as mean ± SE or percentages after adjusting for age, sex, body mass index, smoking status, hyperlipidemia, duration of hypertension, daily dose of doxazosin, and 24-h systolic blood pressure using analysis of covariance.

<28 mm Hg, n = 73). In the Surge group, those with higher α-adrenergic MBPS (n = 17) had a markedly higher frequency of multiple SCI, whereas none in the lower α-adrenergic Surge group had multiple SCI (n = 7) (77% v 0%, P = .001; Fig. 2). In addition, the slope between MBPS and α-adrenergic MBPS (Fig. 2) was significantly steeper in patients with multiple SCI than in those without multiple SCI, even after controlling for 24-h BP (P < .05).

Table 4 shows the results of adjusted MBPS and α-adrenergic MBPS using ANCOVA. Even after adjusting for possible confounding variables, MBPS and α-adrenergic MBPS were significantly higher in the multiple SCI group than in the nonmultiple SCI group. Table 5 shows the results of a logistic regression analysis using MBPS and α-adrenergic MBPS as continuous variables in the total sample. After adjusting for possible confounding variables, both MBPS (model 1) and α-adrenergic MBPS (model 2) were significantly associated with multiple SCI. However, when both were entered in the same model (model 3), only α-adrenergic MBPS remained significant. These surges were also significantly associated with SCI (one ore more SCI per person: 10 mm Hg MSBP increase: OR = 1.44, P = .03; 10 mm Hg α-adrenergic MBPS increase: OR = 1.55, P = .006). There were no significant associations between the morning surge in pulse rate and either single or multiple SCI.

Discussion

This study, has demonstrated a positive association between the MBPS, particularly the component associated with α-adrenergic activity, and silent hypertensive cerebrovascular disease in elderly individuals. This finding is supported by the relatively high reproducibility of MBPS in the two baseline recordings, and the fact that we used the average of these to reduce regression to the mean when assessing the effects of the α-adrenergic blocking drug doxazosin.

Morning BP Surge

The Surge group in this study had a higher number of SCI and higher prevalence of multiple SCI than the Nonsurge group, whereas there was no significant difference in the clinic and average 24-h BP between the two groups. In addition, when we considered the MBPS as a continuous variable, MBPS was significantly correlated with the number of SCI independent of other possible confounders including 24-h SBP level. These results indicate that factors other than persistent BP overload may be involved in the progression of SCI in hypertensive individuals. The SCI occurs predominantly in the small cerebral vessels. An excessive morning BP surge might facilitate microvascular remodeling in the small cerebral arteries through increased shear stress. In addition, platelets may be acti-

Table 3. Determinants of morning blood pressure (BP) surge

Measure	Morning BP Surge*	α-Adrenergic Morning BP Surge†
Age (y)	0.06	0.05
Male (female = 0, male = 1)	−0.11	−0.11
Body mass index (kg/m^2)	0.04	0.01
Duration of hypertension (y)	−0.003	0.12
Dose of doxazosin (mg/day)	−0.09	−0.06
Left ventricular hypertrophy (absence = 0, presence = 1)	0.06	0.10
Silent cerebral infarct (number/person)	0.26‖	0.38‡

Spearman correlation coefficients shown.

* Morning systolic BP minus lowest systolic BP during sleep.

† Reduction in morning systolic BP surge by doxazosin (average of first and second morning BP surge minus third morning BP surge).

‡ P < .001; § P < .01; ‖ P < .05.

Table 4. Adjusted morning blood pressure (BP) surge status and multiple silent cerebral infarct (SCI)

Measure	Multiple SCI Group (n = 24)	Nonmultiple Surge Group (n = 74)	P
Systolic BP			
Morning BP surge*	38.6 ± 2.5	30.1 ± 1.9	.011
α-Adrenergic morning BP surge†	21.7 ± 2.6	7.2 ± 2.0	< .001
Diastolic BP			
Morning BP surge*	19.9 ± 1.5	15.9 ± 1.1	.037
α-Adrenergic morning BP surge†	6.6 ± 2.1	1.6 ± 1.5	.073

Data shown as mean ± SE, after adjusting for age, sex, body mass index, smoking status, hyperlipidemia, duration of hypertension, dose of doxazosin, and 24-h systolic BP, using analysis of variance.
* Morning systolic BP minus lowest systolic BP during sleep.
† Average of first and second morning BP surge minus third morning BP surge.

vated by increased shear stress[16] and by increased sympathetic tone (an α_2-receptor mediated effect).[17] Thus, in atherosclerotic arteries, platelet activation in the morning hours could contribute to the formation of microthrombus.

Determinants of Alpha Adrenergic Morning BP Surge

We defined the α-adrenergic component of the MBPS as the reduction of MBPS by doxazosin therapy. The α-adrenergic MBPS varied widely among individual patients, even within the MS group, suggesting that the mechanism of MBPS is heterogeneous. The function of the human sympathetic nervous system is altered in important ways by aging. Microneurographic recording from sympathetic fibers and studies of spillover of the sympathetic neurotransmitter norepinephrine to plasma suggest that progressive sympathetic activation occurs with aging,[7] although the sympathetic α-adrenergic vasoconstrictor responsiveness to endogenous norepinephrine release has been found to be reduced with age in healthy men.[18] Thus α_1-adrenergic blocker therapy might be especially useful for elderly hypertensive patients whose BP level is predominantly dependent on increased sympathetic activity. In fact, the previous results of the HALT study indicated that the doxazosin was more effective in older than in younger hypertensive persons.[7,8]

Alpha Adrenergic Morning BP Surge and Cerebrovascular Disease

The α-adrenergic MBPS was positively associated with the number of SCI in the multiple logistic regression analysis, independently of age, 24-h BP, and other confounding variables. A general characteristic of antihypertensive drugs is that the greater the baseline BP level, the greater the BP reduction. Thus the α-adrenergic morning BP surge, defined by the BP response to doxazosin, would partly depend on the baseline morning BP surge level. The morning surge is not exclusively mediated by the α-adrenergic sympathetic system, as it can also be controlled by a nonspecific, appropriately timed intervention such as extended release verapamil.[19] However, in our study, the difference in the slopes of the baseline morning BP surge and the BP response to doxazosin (Fig. 2) between subjects with multiple SCI and those without multiple SCI may indicate that there is some α-adrenergic role in the pathogenesis of silent hypertensive cerebrovascular disease. In addition, when we entered the MBPS and α-adrenergic MBPS into the same model, only the

Table 5. Multiple logistic regression analysis for multiple silent cerebral infarcts

Covariate	Model 1 Odds Ratio (95% CI)	Model 1 P	Model 2 Odds Ratio (95% CI)	Model 2 P	Model 3 Odds Ratio (95% CI)	Model 3 P
Morning BP surge (10 mm Hg)*	1.63 (1.13–2.34)	.008	—		0.98 (0.58–1.64)	.935
α-Adrenergic morning BP surge (10 mm Hg)†	—		1.93 (1.35–2.76)	.0003	1.96 (1.21–3.16)	.006

Adjusted odds ratios of the presence of multiple (more than two per person) silent cerebral infarcts after adjusting for age, sex, body mass index, smoking status, hyperlipidemia, 24-h systolic BP, and daily dose of doxazosin.
* Morning systolic BP minus lowest systolic BP during sleep.
† Average of first and second morning BP surge minus third morning BP surge.
BP = blood pressure; CI = confidence interval.

α-adrenergic MBPS remained significantly correlated with SCI. In the Surge group, subjects with higher α-adrenergic surge had a markedly higher frequency of multiple SCI, whereas none in the lower α-adrenergic Surge group had multiple SCI. Because this was a cross-sectional study, the causal relationships between the various factors remain unclear. Increased sympathetic activity could accelerate the progression of SCI formation through increased morning BP surge and other pathways such as platelet hyperactivation, endothelial cell dysfunction, and increased blood viscosity.[1,2] On the other hand, the presence of multiple SCI might itself increase the morning BP surge by altering central sympathovagal balance toward increased sympathetic activity. Thus sympathetic activity is increased in patients with clinically overt ischemic cerebrovascular disease, as manifested by increased plasma norepinephrine levels, which may be an independent risk factor for future cardiovascular and cerebrovascular events.[12] In a study using muscle sympathetic nervous activity recording, sympathetic nervous activity was higher in the patients with cerebrovascular disease than in control subjects, suggesting that the damage of cortical or subcortical structures might cause an increase in basal sympathetic activity.[10] In our previous study, heart rate variability, an indicator of autonomic nervous function, was diminished in hypertensive patients with multiple SCI.[20]

Study Limitation

This study lacks specific data for other antihypertensive drugs. The renin-angiotensin system,[21] which also exhibits a morning surge,[22] could also contribute to the BP surge. Thus, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, particularly if administered to patients just before they go to bed, may suppress the morning BP surge. Labetalol,[23] an α/β blocker, and extended-release verapamil taken at bedtime[19] also blunt the morning BP surge. Because our data suggest that the morning surge in sympathetic activity may have detrimental effects, it is possible that patients may benefit from treatments that inhibit this surge, either by central or peripheral blockade of the α-adrenergic limb of the sympathetic nervous system. At the same time it should be borne in mind that in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the rate of hospitalization for congestive heart failure was doubled in patients in the doxazosin arm compared with the chlorthalidone arm,[24] and there was also a slightly higher risk of stroke. However, the latter difference could be explained by the lower BP levels in the chlorthalidone group. In reality, most patients who are taking and α-blocker for lowering their BP are likely to be taking a diuretic as well.

In conclusion, our study suggests that an increased morning surge in BP, particularly that dependent on α-adrenergic activity, may be linked to the development of hypertensive cerebrovascular disease.

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AJH 2004; 17:1075–1076

Editorial

Blood Pressure Variability in Hypertension

A Possible Cardiovascular Risk Factor

Kazuomi Kario

There is consensus that an increased blood pressure (BP) level increases the risk for cardiovascular disease. The ambulatory BP level during a 24-h period is more closely associated with advanced hypertensive target organ damage and a poorer cardiovascular prognosis than the clinic BP level. On the other hand, the clinical implication of ambulatory BP variability has not been established as an independent cardiovascular risk predictor.[1] Some studies have found that ambulatory BP variability is a significant and independent determinant of target organ damage,[2,3] and poor cardiovascular prognosis, whereas other investigators have not found an independent association.[4] In population studies, 24-h BP variability and daytime BP variability have been independently associated with left ventricular hypertrophy[3] and cardiovascular mortality,[4] respectively.

Recently, Gómez-Angelats et al[5] demonstrated that in middle-aged untreated hypertensive patients, ambulatory systolic BP variabilities (SD of 24-h BP) assessed by intermittent ambulatory BP monitoring and by noninvasive continuous (beat-to-beat) BP monitoring were significantly associated with brain deep white matter lesion detected by brain magnetic resonance imaging. This deep white matter lesion, a silent cerebral disease, is a predisposing condition of clinical stroke, dementia, depression, and falls in the elderly.[6] In older subjects, increased ambulatory systolic BP variability was also significantly associated with brain atrophy.[7]

The two major determinants of BP variability are age and a high BP level, which are also major cardiovascular risk factors. Thus, the significant impact of BP variability on cardiovascular disease seems to depend partly on age and high BP level. In fact, in a previous study, the significant association between BP variability and cardiovascular risk disappeared after controlling for confounding factors including age and ambulatory BP level.[4] In the study by Gómez-Angelats et al,[5] after adjusting for 24-h BP level, the positive association between BP variability and deep white matter lesion disappeared.

The 24-h ambulatory BP variability includes behavior-induced BP changes[8,9] and specific components of diurnal BP variation, which is a potential risk for cardiovascular disease (Fig. 1).[10–16] These specific components may be more closely associated with hypertensive target organ damage and subsequent cardiovascular events than overall 24-h ambulatory BP variability. Abnormal diurnal BP variation, such as marked nocturnal BP decreases (extreme dippers)[10,11] or exaggerated morning BP surge,[12–14] and reverse diurnal BP variation patterns with higher sleep BP than awake BP (risers), are risks for target organ damage and cardiovascular events. These phenotypes of ambulatory BP variability are associated with each other and with 24-h ambulatory BP variability.[14,15] Abnormal diurnal BP variability is associated with other relatively shorter BP variability such as orthostatic BP variability in elderly hypertensives.[15]

Various mechanisms may be involved in the association between BP variability and cardiovascular disease. In addition to augmented mechanical stress on the cardiovascular system (which leads to cardiovascular remodeling), increased variability of blood flow by augmented BP variability increases sheer stress on endothelial cells advancing atherosclerosis. Sheer stress-induced platelet activation at atherosclerotic stenotic sites,[17] and subsequent hypercoagulability may lead to cardiovascular events. Neurohumoral activation, which is increased in those with increased BP variability,[18] may also increase the risk for cardiovascular disease.

Clinically, current cardiovascular risk stratification depends on the ambulatory BP level and the status of the target organ damage. In addition to these two major predictors, BP variability may be the possible third axis of risk stratification. Development of a BP monitoring device to detect the specific component of BP variability, reproducibility, and further prospective and interventional studies are necessary to establish the clinical impact of BP variability on target organ damage and cardiovascular events in hypertensive patients.

Received June 16, 2004. First decision June 16, 2004. Accepted June 21, 2004.

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0895-7061/04/$30.00
doi:10.1016/j.amjhyper.2004.06.021

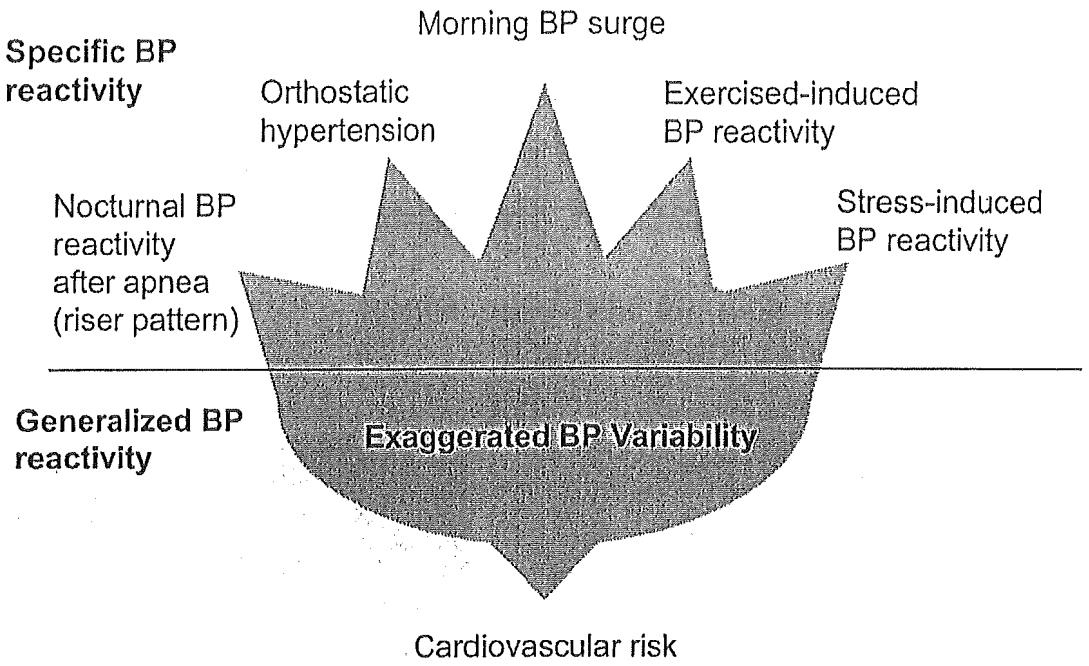

FIG. 1. Phenotypes of ambulatory blood pressure (BP) variability for cardiovascular risk in hypertension.

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AJH 2004; 17:636–637

Case Report

Nocturnal Onset Ischemic Stroke Provoked by Sleep-Disordered Breathing Advanced With Congestive Heart Failure

Kazuomi Kario, Masato Morinari, Mitsunobu Murata, Takaaki Katsuki, and Kazuyuki Shimada

Recently, sleep-disordered breathing and nocturnal hypoxia have been recognized to increase the risk of cerebrovascular disease.[1] Kirkham et al reported that nocturnal hypoxemia was a predictor of future cerebrovascular events in sickle-cell disease.[2] However, it remains unclear whether nocturnal hypoxemic episodes directly lead to nocturnal onset stroke, because other predisposing conditions might confound the association between sleep-disordered breathing and the risk of stroke. Congestive heart failure is often accompanied by central sleep–disordered breathing.[3] We report here a case of nocturnal onset ischemic stroke directly provoked by sleep-disordered breathing, newly developed together with congestive heart failure.

Case Report

The patient was a 67-year-old man who was diagnosed with congestive heart failure April 17, 2001. He had a history of coronary artery bypass grafting because of acute myocardial infarction (three-vessel disease) 11 months previously, as well as Leriche syndrome. He had been given anticoagulation therapy with a prothrombin time of approximately 1.6 international normalized ratio (INR), antiplatelet therapy, nitrate, and long-acting calcium antagonists, and his blood pressure (BP) levels had been controlled from 130 to 160 mm Hg for systolic BP, and from 75 to 90 mm Hg for diastolic BP. Because of the development of mild congestive heart failure, administration of a diuretic (spinoloractone) was started. Mild left hemiparesis and sensory disturbance were present when the patient awakened 15 days after starting diuretic intake, and this neurologic deficit continued until the next morning. One month after the episode, brain magnetic resonance (MR) imaging revealed multiple cerebral infarcts on T2-weighted imaging (Fig. 1A) and flair imaging (Fig. 1B). Diffusion MR imaging revealed a new infarct corresponding to the patient's neurologic deficit (Fig. 1C, arrow). Brain MR angiography showed total occlusion of left internal carotid artery (Fig. 2, arrow). When compared with the BP variables obtained from ambulatory BP monitoring 3 months before the episode, the BP variables 1 month after the episode were significantly lower (after versus before the episode, 24-h BP: 111/70 *v* 125/72 mm Hg; awake BP: 114/72 *v* 133/77 mm Hg; sleep BP: 106/67 *v* 111/66 mm Hg). In addition, over-

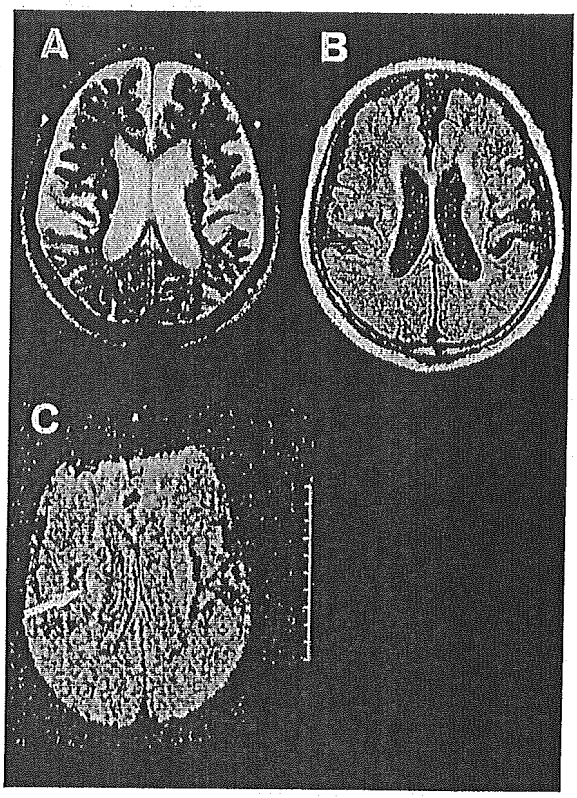

FIG. 1. Brain magnetic resonance (MR) imaging 1 month after the episode revealed multiple cerebral infarcts. (**A**) T2-weighted imaging; (**B**) flair imaging. Diffusion MR imaging revealed a new infarct corresponding to a neurologic deficit (**C, arrow**) in this patient.

Received September 26, 2003. First decision December 16, 2003. Accepted March 2, 2004.

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0895-7061/04/$30.00
doi:10.1016/j.amjhyper.2004.03.667

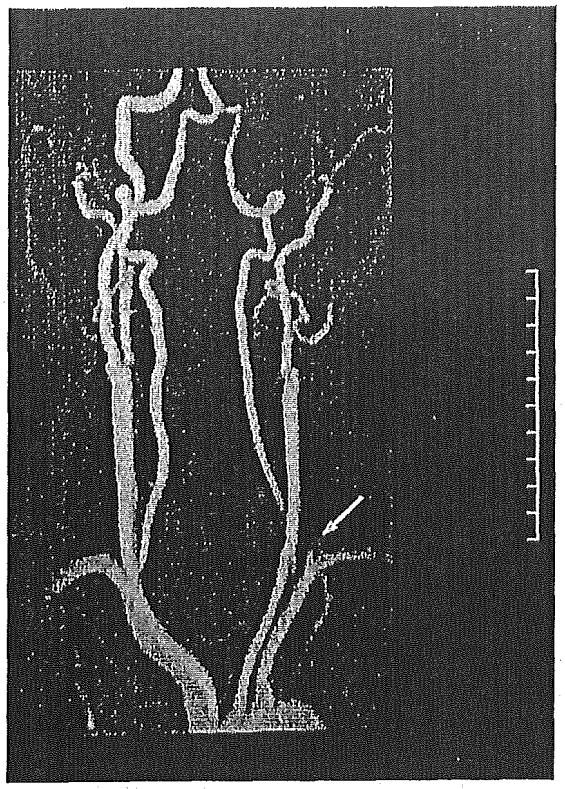

FIG. 2. Brain MR angiography disclosed total occlusion of the left internal carotid artery (**arrow**).

night pulse oximetry one month after the episode newly revealed moderate sleep-disordered breathing with a high frequency of 4% desaturation episodes (29.2/h) during sleep, whereas mean awake oxygen saturation was 97%. Polysomnography disclosed that the patient's apnea–hypopnea index was 55/h (central apnea dominant, 71% of total apnea). Three months before the episode, his frequency of 4% desaturation episodes during sleep had been only 4.8/h.

Discussion

In this patient, MR angiography examination revealed occlusion of internal carotid artery; however, he had noted no clinical neurologic deficits. Thus, we considered that nocturnal hypoxia, which developed along with congestive heart failure, directly triggered transient ischemic attack with a new infarct verified by MR imaging of the brain. A previous case-control study showed that sleep apnea was fivefold more frequent in patients with transient ischemic attack than in a normal control group (62.5% *v* 12.5%).[4] In addition, nocturnal BP reduction (5 mm Hg reduction for systolic BP) caused by a diuretic might reduce cerebral perfusion and trigger a nocturnal ischemic episode. We have recently reported that elderly hypertensive patients with marked nocturnal BP fall (extreme dipping pattern) reduction have a higher risk of stroke than with appropriate nocturnal BP fall (more normal dipping pattern).[5] During an apneic episode, cerebral perfusion pressure was found to decrease by approximately 11.2 ± 7.7 mm Hg (mean ± SD) from baseline,[6] and a significant reduction in middle cerebral artery blood flow velocity has been reported.[7] In addition to the direct effect of hypoxia, these intracranial hemodynamic changes in patients with marginal circulatory reserve would contribute to increase the risk of ischemic stroke.

In this patient, onset of congestive heart failure per se triggered nocturnal hypoxia. The use of diuretic therapy for congestive heart failure may have independently contributed to nocturnal hypoxia. Thus, this implies that initial therapy of heart failure might emphasize nondiuretic options.

In conclusion, if congestive heart failure develops in high-risk patients with severe systemic atherosclerosis, simple evaluation of nocturnal hypoxemic episodes using pulse oximetry should provide valuable information for predicting the risk of stroke.

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AJH 2004; 17:439–445

Sleep Pulse Pressure and Awake Mean Pressure as Independent Predictors for Stroke in Older Hypertensive Patients

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Background: It remains uncertain which is the stronger predictor for stroke in older hypertensives, ambulatory pulse pressure (PP) or mean blood pressure (MBP).

Methods: We studied the prognosis for stroke in 811 older hypertensives in whom ambulatory BP monitoring was performed. We also assessed silent cerebral infarct (SCI) by brain magnetic resonance imaging.

Results: Silent cerebral infarcts were found in 50% of 515 subjects (64% of the total population) in whom we assessed SCI using brain magnetic resonance imaging. During a mean of a 42-month follow-up period, stroke events occurred in 59 subjects. After adjustment for covariates, for each 10 mm Hg increase in sleep PP, there was an independent 43% (95% confidence interval [CI]: 16%–75%, $P = .001$) increase in the stroke risk, and sleep MBP was not a significant factor after controlling for sleep PP. On the other hand, for each 10 mm Hg increase in awake MBP, there was an independent 48% (95% CI: 21%–81%, $P = .0002$) increase in the stroke risk, and awake PP was not a significant factor after controlling for awake MBP. After adjusting for SCI (a strong predictor, $P < .0001$) at baseline, the effects of awake MBP (38% risk increase for each 10 mm Hg, $P = .007$) and sleep PP (32% risk increase for each 10 mm Hg, $P = .016$) remained significant.

Conclusions: In older hypertensives, the impacts of PP and MBP on stroke risk are different during sleep and awake periods. Sleep PP and awake MBP are both predictors of stroke events independently of SCI. Am J Hypertens 2004;17:439–445 © 2004 American Journal of Hypertension, Ltd.

Key Words: Ambulatory pulse pressure, hypertension, prognosis, silent cerebral infarct, elderly.

Recently, there is growing evidence that arterial stiffness is a predictor for cardiovascular events and death.[1–3] Pulse pressure (PP), which is a pulsatile component of blood pressure (BP), is one of the indicators of arterial stiffness. Many prospective studies have shown that PP is an important predictor of cardiovascular risk, and some studies have demonstrated that PP is a stronger predictor of cardiovascular events than mean BP (MBP; steady component), particularly in an elderly population.[4–6] However, most of these prospective studies showed that PP is an independent predictor of cardiovascular event used casual BP. Although ambulatory BP is known to be more closely associated with silent target organ damage and cardiovascular risk than clinic BP, there has been only a few prospective studies on the association between ambulatory PP (APP) and cardiovascular risk.[7–9]

Recently, silent cerebral infarct (SCI) is often detected by brain magnetic resonance imaging (MRI) in older subjects, particularly in those with hypertension.[10–12] Silent cerebral infarct is the strongest predictor of subsequent clinically overt stroke.[11,12] The association between APP and stroke risk might be related to SCI, and the stroke risk might be augmented when elevated APP is accompanied by SCI.

To investigate whether APP is a risk factor for stroke in relation to SCI in older hypertensives, we prospectively studied the stroke prognosis in 811 older hypertensive Japanese patients in whom ambulatory BP monitoring (ABPM) was performed in the absence of antihypertensive treatment.

Received October 7, 2003. First decision November 19, 2003. Accepted January 7, 2004.

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This study was supported by a Grant-in-Aid (1992–2001) from the Foundation for the Development of the Community (KK), a Research Grant for Cardiovascular Medicine (14-6) from the Ministry of Health, Labor and Welfare (KK), and a Research Grant (C-2) from the Ministry of Education, Science, and Culture (KK), Japan.

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0895-7061/04/$30.00
doi:10.1016/j.amjhyper.2004.01.001

Methods

Subjects

This study is based on 811 older subjects (>50 years of age) diagnosed with essential hypertension, who are the participants of Jichi Medical School ABPM Study Wave 1.[12] This represents 99% of the 821 subjects who were initially enrolled in the study from six participating institutes (three clinics, two hospitals, and one outpatient clinic of the university hospital) between January 1, 1992, and January 1, 1998. No patient had taken any antihypertensive medication for at least 14 days before the ABPM study, but 51% had a prior history of antihypertensive medication. All of the subjects studied were ambulatory, and all gave informed consent for the study. We excluded from this study patients with renal failure (serum creatinine level ≥176 mmol/L) or hepatic damage, with obvious present illness, or with past history of coronary artery disease, stroke (including transient ischemic attacks [TIA]), congestive heart failure, or arrhythmia. Of the 811 patients, 515 (64%) agreed to and had a brain MRI. There were no significant differences in the age, gender, PP, or MBP parameters at the baseline, or in the incidence of cardiovascular disease between these 515 subjects and the other 296 subjects without brain MRI examination. This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, Japan. All the results of the ABPM and brain MRI were returned to the physicians who followed up the subjects.

Twenty-four-hour ABPM

Noninvasive ABPM was carried out on a weekday with one of three automatic ABPM devices (ABPM-630, Nippon Colin Co., Aichi; TM-2421 or TM-2425, A&D Co., Tokyo, Japan), which recorded BP (by the oscillometric method) and heart rate every 30 min for 24 h. We excluded the subjects in whom we obtained valid BP readings in <80% of either awake or asleep attempts, and those who reported in our post-ABPM questionnaire that their sleep was severely disturbed by wearing the ABPM. Sleep BP was defined as the average of BPs from the time when the patient went to bed until the time he/she got out of bed, and awake BP as the average of BPs recorded during the rest of the day.

Brain MRI

Brain MRI was carried out using a superconducting magnet with a main strength of 1.5T (MRT200FXII, Toshiba, Tokyo; SIGNA-HorizonVer.5.8, General Electric Co., Tokyo; or Vision, Siemens, Tokyo, Japan) within 3 months of the ABPM. T1-weighted images and T2-weighted images were obtained in the transverse plane with 7.8- to 8.0-mm thick sections. An SCI was defined as a low signal intensity area (3 to 15 mm) on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images, as described previously.[10,12,13] Multiple SCI was defined as ≥2 SCIs in a person. The MRI images of the subjects were randomly stored and interpreted blind to the subjects' name and characteristics. The interclass (non-SCI = 0, one SCI = 1, multiple SCIs = 2) kappa statistics were 0.70 and 0.80 for inter-reader and intrareader, respectively, in our laboratory.

Follow-up and Events

The patients' medical records were intermittently reviewed after the subjects entered the study for drug therapy and the occurrence of cardiovascular events. The follow-up evaluation was performed during a 20-month period from 1996 to 1998, and the mean follow-up period was 42 months, with a range from 1 to 68 months. If subjects stopped coming to the clinic, we conducted telephone interviews. Events were classified as cardiac events, stroke events, and noncardiovascular deaths. Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke, but excluded TIA (transient neurologic deficits that disappear within 24-h after the onset). Cardiac events included fatal and nonfatal acute myocardial infarction, unexplained sudden death within 6 h of the abrupt onset of symptoms, and coronary revascularization. Fatal event was defined when death occurred within 1 month from the event. These events were accepted if documented in the medical records, or if confirmed by a general practitioner. We excluded 15 possible TIA from the stroke events. Of the total 821 eligible subjects at baseline, follow-up was achieved in 811 (99%) subjects, and the data analysis was restricted to these subjects.

Statistical Analysis

Data are expressed as the mean (SD). One-way ANOVA was performed to detect differences among groups in mean values, and the χ^2 test was used to detect differences among groups in prevalence rates. Adjusted odds ratio and 95% confidence intervals (95% CI) for baseline SCI were calculated using stepwise multiple logistic analysis, and adjusted relative risks (RR) and 95% CI for future stroke risk were calculated using forced or stepwise Cox regression analysis. For the subjects who experienced multiple nonfatal cardiovascular events, the analysis included only the first stroke event. These statistical analyses were performed using SPSS version 8.0 (SPSS Inc., Chicago, IL). Differences with $P < .05$, two-tailed, were considered statistically significant.

Results

During the 42-month follow-up period, 59 clinically overt stroke events (38 ischemic strokes, 9 hemorrhagic strokes, 12 unknown subtype), and 20 fatal cardiovascular events (13 fatal strokes and 7 fatal cardiac events) occurred. At the time of the final follow-up, 426 (53%) of the total 811 patients were receiving antihypertensive medications (diuretics, α- or β-blockers, calcium antagonists, or angio-