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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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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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Diabetic Brain Damage in Hypertension

Role of Renin-Angiotensin System

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Abstract—Diabetes and hypertension are potent risk factors for cerebrovascular disease. We studied the effects of an angiotensin II type 1 receptor blockade (ARB) on brain damage in hypertensives in relation to diabetes. We studied cerebral metabolism (by proton magnetic resonance spectroscopy) and hemodynamics (by phase-contrast magnetic resonance angiography) before and 3 to 4 months after candesartan therapy in 20 diabetic hypertensives (DHTs) and 20 matched nondiabetic hypertensives (HTs). Silent multiple cerebral infarcts detected by brain MRI were more common in DHTs than in HTs (50% versus 25%). Cerebral *N*-acetyl aspartate (NAA; an indicator of functional neuronal mass) was lower in DHTs than in HTs (8.35 versus 9.58 mmol/kg; $P=0.007$). Baseline quantitative volume flow in the internal carotid arteries (ICAs) and the middle cerebral arteries (MCAs) was comparable between the 2 groups, whereas cerebrovascular reserve (CVR) assessed using acetazolamide (a cerebral arteriolar dilator) in ICAs (25% versus 35%; $P=0.03$) and MCAs (20% versus 31%; $P=0.01$) was lower in DHTs than in HTs. These baseline CVR and NAA values of DHT group were lower than those of 12 matched normotensives (CVR: 44% for ICA; 41% for MCA; NAA: 10.5 mmol/kg; all $P<0.005$). After candesartan therapy, CVR in ICAs and MCAs was significantly increased ($P=0.001$) independently of the reduction of the 24-hour blood pressure level, whereas the cerebral NAA level did not change. In conclusion, brain damage is advanced in DHTs. ARB partly improved the impaired cerebral microvascular function in DHTs. (***Hypertension*. 2005;45:887-893.**)

Key Words: metabolism ■ circulation ■ receptors, angiotensin ■ blood pressure

Diabetes is an independent major risk factor for cardiovascular events.[1,2] In addition, cardiovascular mortality associated with mild systolic hypertension (140 to 159 mm Hg) compared with normal systolic blood pressure (BP; <140 mm Hg) is highly dependent on the glycemic status.[3] Diabetes has been shown to be a strong independent risk factor for stroke and is associated with an ≈1.8- to 6-fold increase of the risk of stroke.[1] Diabetes is also associated with either an accelerated cognitive decline or an increased incidence of dementia.[4] In our study on asymptomatic hypertensives, those having diabetes were found to be more likely to have advanced silent cerebral infarct (SCI) than those without diabetes.[5] This silent cerebrovascular disease is a specific predictor not only for future stroke events but also for dementia.[6,7]

Recent biochemical, physiological, and functional studies have suggested that the brain renin-angiotensin system (RAS) is regulated independently of the peripheral RAS.[8] Angiotensin II type 1 (AT_1) and type 2 (AT_2) receptors have been identified in the brain. Selective nonpeptide AT_1 receptor blockers (ARBs), applied systemically, have been shown to inhibit peripheral and brain AT_1 receptors. Inhibition of brain AT_1 receptors may contribute to the BP-lowering effects of ARBs. In animal models, blockade of brain and cerebrovascular AT_1 receptors by ARBs prevents the reduction in blood flow during brain ischemia, reduces the volume of ischemic injury, and improves neurological outcome after brain ischemia.[9,10] In addition, animal studies have shown that ARBs enable endogenous angiotensin II to stimulate neuronal regeneration via activation of AT_2 receptors.[11] Although the relationship between the tissue RAS and diabetic macrovascular and microvascular disease is well established,[12] the effects of ARBs on cerebral metabolism and hemodynamics have not been fully investigated.

Recently developed magnetic resonance spectroscopy (MRS) methods can detect cerebral metabolites noninvasively.[13–15] *N*-acetyl aspartate (NAA) is located only in neurons and their axons. Thus, cerebral NAA is considered to be an indicator of the functional neuronal mass and axons, and reduced NAA has been reported in patients with several cerebral diseases, such as atherosclerotic cerebral disease.[13] Phase-contrast magnetic resonance angiography (PC-MRA) can noninvasively assess cerebral hemodynamics[16,17] and cerebrovascular reserve (CVR) when combined with acetazolamide, a cerebral vasodilator.[18,19]

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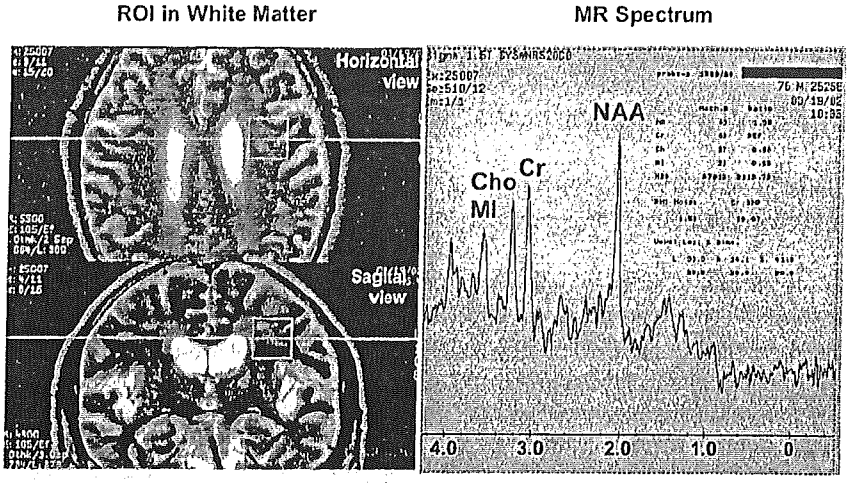

Figure 1. Region of interest (ROI) of MRS in deep white matter (left) and MRS spectrum (right) of DHT patient with advanced white matter lesion. NAA, 6.23 mmol/kg; creatine (Cr), 4.87 mmol/kg; choline (Cho), 1.33 mmol/kg. MI indicates myoinositol.

In this study, we evaluated cerebral metabolism and hemodynamics in asymptomatic hypertensives with and without diabetes using MRS and PC-MRA, respectively, and examined the effects of the ARB candesartan on these cerebral parameters.

Methods

Subjects

The study subjects were 20 outpatients who were newly diagnosed hypertensive patients (clinic systolic BP [SBP] ≥140 mm Hg; or diastolic BP [DBP] ≥90 mm Hg) with type 2 diabetes (diabetic hypertensive [DHT] group) and 20 age- and sex-matched mild hypertensives without diabetes (nondiabetic hypertensive [HT] group). We also consecutively recruited 12 age- and sex-matched normotensive (NT) controls with clinic SBP <140 mm Hg and DBP <90 mm Hg, and with 24-hour SBP <120 mm Hg and 24-hour DBP <90 mm Hg (NT group). These subjects were recruited from the participants who underwent a health check examination. The period of the recruitment of this study was from October 2001 to January 2003.

Clinic BP was measured after patients had rested for at least 5 minutes in a sitting position, and the average of 3 consecutive measurements on 2 different days was used as clinic BP. Diabetes was newly diagnosed according to fasting glucose >7.73 mmol/L (139 mg/dL) or a 2-hour postload serum glucose >11.1 mmol/L (199 mg/dL) in all other cohorts, in accordance with the 1985 World Health Organization (WHO) criteria for diabetes.[20] Fasting glucose of all the nondiabetic subjects (HT and NT groups) was <6.11 mmol/L (110 mg/dL), and the 2-hour postload glucose was <7.77 mmol/L (140 mg/dL). Exclusion criteria of all the DHT, HT, and NT groups included renal failure (serum creatinine level >176 μmol/L [2.0 mg/dL]), hepatic damage, obvious present illness, a past history of coronary artery disease, stroke (including transient ischemic attacks), or arrhythmia (including atrial fibrillation). Hyperlipidemia was defined as a total cholesterol level >6.21 mmol/L (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 (in kilograms)/height (in meters).[2]

Study Protocol

We studied the 24-hour ambulatory BP monitoring (ABPM), cerebral hemodynamics (by PC-MRA), and metabolism (by proton MRS) at the baseline in the DHT, HT, and NT groups. We also repeated the same procedure 3 to 4 months after candesartan therapy in the DHT and HT groups. Patients were started on 8 mg candesartan daily, taken in the morning. The dose was increased to 12 mg daily (the maximum dose permitted for use in Japan) after 2 weeks, regardless of the degree of BP reduction. This study was approved by the research ethics committee of the Department of Cardiology, Jichi Medical School, Japan, and all subjects studied gave informed consent.

Twenty-Four–Hour ABPM

Noninvasive ABPM was performed on a weekday with an automatic device (TM-2425; A&D Co., Inc.) that recorded BP and pulse rate every 30 minutes for 24 hours.[7] The ambulatory BP data used in the present study were those obtained by the oscillometric method.

Brain MRI

Brain MRI was performed using a superconducting magnet with a main strength of 1.5T (SIGNA-Horizon version 5.8; General Electric). T1- and T2-weighted images were obtained in the transverse plane with 7.8-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.[7,21] SCI as defined above might include lesions other than true infarcts, such as unidentified bright objects and état criblé, dilated perivascular spaces, especially if they are <5 mm.[21] The number of SCIs per patient was counted, and multiple SCIs were defined as ≥2 infarcts. All SCIs detected were lacunar infarcts with a size of <15 mm. The MRI images of the subjects were stored randomly and interpreted blind to the subjects' names and characteristics. The κ-statistics assessing inter-reader and intrareader agreement (non-SCI, 1 SCI, and multiple SCIs) were 0.70 and 0.80, respectively, in our laboratory.

Periventricular hyperintensities on T2-weighted images were classified into 4 grades, as described and illustrated previously.[21] Briefly, grade I was defined as no abnormality or minimal periventricular signal hyperintensities in the form of caps confined exclusively to the anterior horns or rims lining the ventricle; grade II as caps in the anterior and posterior horns of the lateral ventricles or periventricular unifocal patches; grade III as multiple periventricular hyperintense punctate lesions and their early confluent stages; and grade IV as multiple areas of high signal intensity that reached confluence in the periventricular region. All of the magnetic resonance images were interpreted under blind conditions by 2 of the authors. Because only 2 patients showed grade IV, these patients and those with grade III were considered together as showing advanced white matter lesions.

Proton MRS

Proton MRS was performed in the left deep white matter area using a GE 1.5T Sigma system using a standard quadrature bird-cage head coil. A single voxel was located in the same area (defined by the horizontal and coronal sections of T2-weighted MRI) of the left periventricular deep white matter (voxel volume 8 mL) as described previously (Figure 1, left).[13] Shimming of the magnetic field was performed, and then stimulated echo acquisition mode spectroscopy

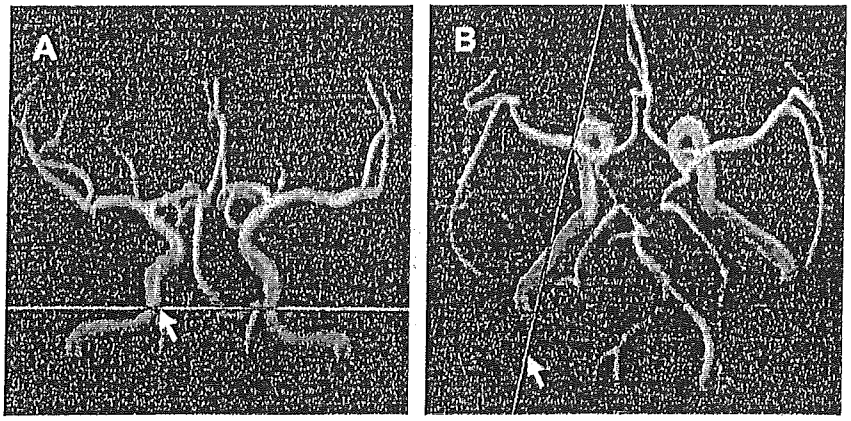

Figure 2. Portions of the ICAs (A) and MCAs (B) for quantitative MRA volume flow assessed by nontriggered PC-MRA.

was performed at short echo times (echo time [TE] 30 ms; repetition time [TR] 1500 ms) using the automated spectroscopy protocol of the manufacturer. Peaks with known chemical shifts were identified as follows: NAA, 2.0 parts per million (ppm); creatine, 3.0 ppm; choline, 3.2 ppm (Figure 1, right). The absolute concentrations of the cerebral metabolites were calculated using the brain water signal as an internal reference and expressed as mmol/L per kilogram wet weight, according to the method described previously.[15]

Phase-Contrast Magnetic Resonance Angiography

Quantitative MRA volume flow in the internal carotid arteries (ICAs) and the middle cerebral arteries (MCAs) was assessed by nontriggered PC-MRA, which is a fast, noninvasive, and widely available method to determine blood flow in the major cerebral arteries.[17,18] The MRA measurements in the present study were made using a previously developed and optimized protocol.[16] Measurement of flow in the ICAs (right and left) was performed at the level of the base of the skull (TR/TE 16/9 ms; 8 signals acquired; velocity-encoded cine [V_{enc}] 100 cm/s; Figure 2A). On the basis of an axial 3D time-of-flight MRA scan of the circle of Willis, 2 flow measurement slices were positioned perpendicular to the left and right MCA (TR/TE 17/10 ms; 24 signals acquired; V_{enc} 70 cm/s; Figure 2B). Volume flow values were obtained by integrating across a manually drawn region of interest enclosing the vessel lumen.

CVR was assessed as the percent increase in volume flow of ICAs and MCAs 10 minutes after administration of 500 mg of acetazolamide (an arteriolar dilator).[18] There was no significant difference in BP before and after acetazolamide administration, as shown previously.[19] Because there was no significant stenosis (≥75%) in ICAs or MCAs detected by MRA, the values of volume flow and CVR taken were the averages of the values of the right and left sides.

Statistical Analysis

The 2-sided unpaired t test and χ^2 test were used to test differences between the 2 groups for the mean values of continuous measures and prevalence rates, respectively. One-way ANOVA was performed to evaluate differences among groups, and Tukey's honestly significant difference test was used for comparison of the mean baseline values for pairs of groups (Tables 1 and 2). Repeated-measures ANOVA with Bonferroni's test was used to detect statistically significant changes over time (before and after candesartan therapy) in cerebral parameters between the DHT and HT groups with 24-hour systolic BP as a covariate. Pearson's correlation coefficient was used to assess the relationships between continuous measures. Multiple linear regression analysis was used to study the independent association between cerebral NAA and CVR with the presence of diabetes and 24-hour BP level. The statistical calculations were performed using SPSS version 8.0J (SPSS). Differences/associations with a 2-tailed P value <0.05 were considered statistically significant.

Results

Patient Characteristics

There were no significant differences in the clinical characteristics among the 3 groups (Table 1). The clinic and 24-hour BP levels were comparable between the DHT and HT groups.

Silent Cerebrovascular Disease

SCIs and advanced white matter lesions detected by brain MRI tended to be more common in the DHT than the HT and NT groups, but there was no significant difference among the groups (Table 2).

Cerebral Metabolism

Cerebral NAA was significantly lower in the DHT than in the HT and NT groups (Table 2), whereas there were no significant differences in the other metabolites examined. The cerebral NAA/creatine ratio was also significantly lower in

TABLE 1. Clinical Characteristics of Diabetic and Nondiabetic Hypertension Groups

Variable	DHT Group (n=20)	HT Group (n=20)	NT Group (n=12)	*P* Value*
Age, years	69±9.2	69±9.2	69±9.4	0.989
Men, n (%)	7 (35)	7 (35)	4 (33)	0.995
BMI, kg/m²	24.5±3.4	23.5±3.1	24.1±3.5	0.601
Smoking, %	7 (35)	5 (25)	2 (17)	0.527
Hyperlipidemia, %	7 (35)	5 (25)	2 (17)	0.527
Statin use, %	5 (25)	4 (20)	2 (17)	0.852
ECG-LVH, %	3 (15)	2 (10)	0 (0)	0.393
Proteinuria, %	2 (10)	2 (10)	1 (5)	0.538
Clinic SBP, mm Hg	161±15†	158±11†	123±8.3	<0.001
Clinic DBP, mm Hg	85±10†	84±9.4†	70±7.6	<0.001
Clinic pulse rate, bpm	73±9.7	72±11	72±7.7	0.924
24-hour SBP, mm Hg	139±14†	136±15†	112±6.4	<0.001
24-hour DBP, mm Hg	78±10‡	78±7.5‡	67±6.2	0.001
24-hour pulse rate, bpm	67±9.3	67±5.6	65±5.1	0.685

Data are shown as the mean±SD or the No. (percentage).

*Overall P values for 3 group comparisons of means (ANOVA F-test) or percentages (χ^2 test).

†$P<0.001$, ‡$P<0.01$ vs NT group.

ECG-LVH indicates left ventricular hypertrophy detected by ECG.

TABLE 2. Cerebral Parameters in Diabetic and Nondiabetic Hypertension Groups and NTs

Variable	DHT Group (n=20)	HT Group (n=20)	NT Group (n=12)	P Value*
SCI				
No./person	2.2±2.4‡¶	0.9±1.3	0.5±0.8	0.015
Any infarct, n (%)	12 (60)	8 (40)	4 (33)	0.279
Multiple infarcts*, n (%)	10 (50)	5 (25)	3 (25)	0.191
White matter lesion				
Advanced lesion, n (%)	7 (35)	4 (20)	2 (17)	0.426
Cerebral metabolites				
NAA, mmol/kg	8.35±1.42†§	9.58±1.31	10.5±0.84	<0.001
NAA/creatine ratio	1.28±0.13§	1.39±0.13	1.50±0.20	0.001
Creatine, mmol/L per kg	6.49±0.86	6.90±0.97	7.03±0.64	0.171
Choline, mmol/L per kg	2.01±0.31	2.05±0.45	1.84±0.22	0.253
Cerebral volume flow, mL/min				
ICAs	292±73	263±49	288±56	0.289
MCAs	172±36	155±32¶	186±33	0.040
CVR, %				
ICAs	24.9±14.2‖	35.3±15.6	43.7±13.1	0.003
MCAs	20.1±13.5§	30.9±12.2	41.1±19.7	0.001

Data are shown as the mean±SD or the No. (percentage).
*Overall P values for 3 group comparisons of means (ANOVA F-test) or percentages (χ^2 test).
†$P<0.01$, ‡$P<0.05$ vs HT group; §$P<0.001$, ‖$P<0.01$, ¶$P<0.05$ vs NT group.

the DHT than in the NT group, and it tended to be lower in the DHT than in the HT group ($P=0.06$) (Table 2).

Cerebral Hemodynamics

Baseline quantitative volume flows in the ICAs and the MCAs were comparable among the 3 groups, except that there was lower MCA flow in the HT group than in the NT group (Table 2). The CVRs in ICAs (25% versus 35%; $P=0.07$) and MCAs (20% versus 31%; $P=0.06$) tended to be lower in the DHT than in the HT group, and CVR in the DHT group was significantly lower than that in the NT group ($P<0.05$). Neither baseline cerebral blood flow nor CVR in ICAs and MCAs was significantly correlated with a reduction in cerebral NAA (data not shown).

Diabetes and 24-Hour BP Level Effects on Cerebral NAA and CVR

We studied the effect of diabetes and 24-hour BP on the cerebral NAA and CVR in the total subjects (n=52) in the DHT, HT, and NT groups. After adjusting for other clinical characteristics (age, sex, BMI, and status of smoking and hyperlipidemia), cerebral NAA was independently associated with diabetes (standardized $\beta=-0.466$; partial $R^2=0.182$; $P<0.001$), but it was not significantly associated with 24-hour SBP level ($P=0.279$). After adjusting for other clinical characteristics, CVR in ICAs (standardized $\beta=-0.389$; partial $R^2=0.127$; $P=0.011$) and CVR in MCAs (standardized $\beta=-0.380$; partial $R^2=0.121$; $P=0.007$) were independently associated with diabetes, and CVR in MCAs was marginally associated with 24-hour SBP level (standardized $\beta=-0.261$; partial $R^2=0.059$; $P=0.055$).

Candesartan Therapy

Although candesartan therapy was well tolerated in 37 patients, 3 patients developed dizziness during candesartan therapy; however, because the BP reduction in these patients was mild, we did not discontinue medication. The data were successfully obtained from all 40 patients after candesartan therapy.

After candesartan therapy, CVRs in ICAs and MCAs were significantly increased in the DHT and HT groups, and these increases were significantly greater in the DHT group than in the HT group, even after controlling 24-hour systolic BP (ICAs $P=0.03$; MCAs $P=0.015$; Table 3). On the other hand, the cerebral NAA level did not change. The increases in CVRs in ICAs and MCAs were independent of the reduction of for the 24-hour BP level (Figure 3).

Discussion

This is the first study that assessed the cerebral metabolism and hemodynamics simultaneously in DHTs and HTs, and clarified that in DHT patients, brain damage is more advanced than that in HTs. The reduced levels of neuronal mass and CVR found in DHTs were predominantly determined by the presence of diabetes and independent of 24-hour BP level; however, they were independent of each other.

Reduced Neuronal Mass

Cerebral NAA, an indicator of functional neuronal mass and axons,[13,14,22,23] was significantly lower in DHT patients than in HT patients and NT subjects. In previous studies on cerebral metabolism in congestive heart failure patients, occipital NAA was found to be decreased in patients with

TABLE 3. Comparison of Changes in Cerebral Parameters After Angiotensin Receptor Blockade (candesartan) Therapy

Variables	DHT Group (n=20)	HT Group (n=20)
BP, mm Hg		
Clinic SBP	−13.0±−19.7†	−7.7±−13.7‡
Clinic DBP	−5.1±−8.9‡	−0.4±−6.7
24-hour SBP	−7.4±−11.9‡	−2.6±−13.3
24-hour DBP	−3.5±−5.7‡	−3.0±−6.5‡
Cerebral metabolites, mmol/L per kg		
NAA	−0.05±0.53	0.04±0.42
Creatine	−0.13±0.91	0.04±0.51
Choline	0.01±0.19	0.09±0.21
Cerebral volume flow, mL/min		
ICAs	5.5±57.4	6.5±46.4
MCAs	−7.0±42.0	4.3±31.4
Cerebrovascular reserve, %		
ICAs	14.8±13.6*§	5.7±11.9‡
MCAs	20.2±19.0*§	7.3±11.2†

Changes were calculated as the values after candesartan therapy minus the baseline values, and data are shown as the mean±SD.

*$P<0.001$, †$P<0.01$, ‡$P<0.05$ are the values after candesartan therapy minus the baseline values, analyzed by the paired t test within each group; §$P<0.05$ vs the HT group by repeated-measures ANOVA with Bonferroni test.

severe heart failure with systolic dysfunction.[22,23] This reduction of cerebral NAA was significantly associated with poor prognosis.[23] The area we investigated in the brain was the deep white matter, which is an ischemia-prone watershed area between the cortical circulation and perforator circulation of the brain. The NAA in this area is predominantly located in axons, and hypertensive ischemic morphological change detected by brain MRI occurs most frequently in this area.[6,14] Previous MRI studies showed that ischemic white matter lesions are associated with cognitive dysfunction, depression, gait disturbance, and future stroke.[6,14] Thus, the reduced NAA in DHTs found in the present study seems to indicate a higher risk for psychocognitive dysfunction as well as cerebrovascular events in these patients. Actually, previous population studies showed that diabetes is associated with either an accelerated cognitive decline or an increased incidence of dementia.[4] The prevalence of advanced white matter lesions tended to be higher in DHTs than in the HTs and NTs; however, there was no statistical significance. The reduction of NAA in deep white matter precedes this morphological change in DHTs.

The mechanism of the alteration of cerebral metabolism in DHTs remains unclear. Because the NAA concentration in white matter was reported to be significantly reduced in patients with symptomatic ICA,[24] we speculated that an impaired cerebral circulation may contribute to neuronal damage. However, neither baseline cerebral blood flow nor CVR in ICAs and MCAs was significantly correlated with the reduction in cerebral NAA. In addition, reduced cerebral NAA was predominantly determined by the presence of diabetes and was independent of 24-hour BP level. The reduced NAA in DHTs may not be directly attributable to impaired cerebral microvessel function or elevated BP level, per se, but rather, may be predominantly attributable to direct adverse effects of diabetes-related activation of the apoptotic cell death pathway that exaggerate brain damage.[25]

Impaired CVR

CVR was significantly lower in the DHT group than in the NT group and marginally lower in the DHT group than in the HT group. The lower CVR in the MCA was determined not only by the presence of diabetes but also tended to be associated with higher 24-hour BP level. CVR is the capacity of cerebral microarteriolar dilation to occur in response to decreased cerebral perfusion pressure to maintain constant cerebral blood flow. Diminished CVR is considered to be a risk factor for stroke,[26,27] Persistent high BP and other factors, such as the RAS and inflammatory reactions, all of which are activated in DHTs, may directly impair cerebral microvessel function.

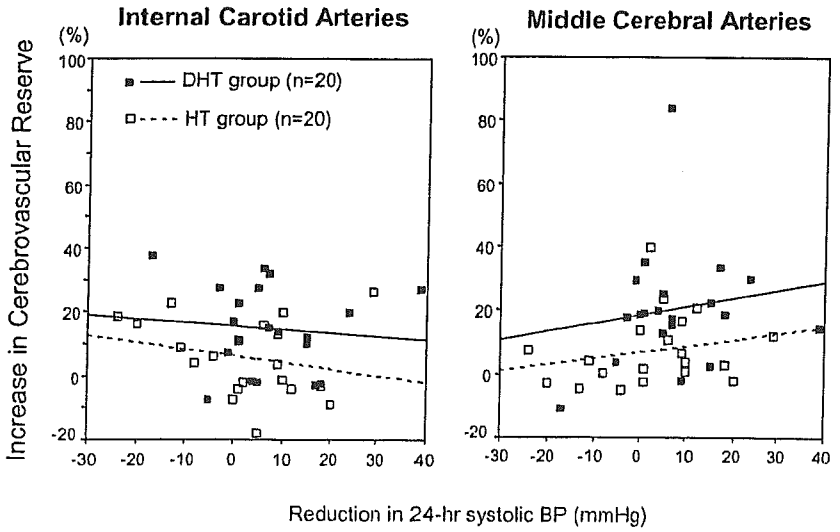

Figure 3. Association between changes of 24-hour systolic BP and CVR after candesartan therapy in DHT and HT groups.

In a recent report, despite effective antihypertensive treatment, resistance arteries from DHT patients showed marked remodeling that was greater than that of vessels from untreated HT subjects.[28]

Effect of ARB on CVR

Candesartan therapy for 3 to 4 months improved the reduced CVRs in ICAs and MCAs in the DHT and HT groups. This favorable effect was significantly greater in the DHT group than in the HT group. This result indicates that the RAS in cerebral microvessels might have some pathogenic role in the impaired CRV in hypertensives, particularly those with diabetes. The increases in CVR in ICAs and MCAs were independent of the reduction of the 24-hour BP level, indicating the BP-independent direct brain-protective effect of ARB. Clinically, this result appears to be in accord with the results of large clinical trials.[29,30] In the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) of high-risk hypertensives, the stroke reduction by ARB was more marked in DHTs than HTs, independent of the BP-lowering effect.[29] The Study on Cognition and Prognosis in the Elderly (SCOPE) demonstrated that nonfatal stroke is reduced by candesartan treatment.[30] In NT rats and spontaneous hypertensive rats, candesartan restored cerebrovascular autoregulation without any influence on baseline cerebrovascular blood flow.[31]

Perspectives

The AT_1 receptor is known to be involved in cognitive function. However, the potential role of ARB in neuroplasticity remains unclear. Oral candesartan treatment very effectively inhibits the centrally mediated effects of angiotensin II, indicating that candesartan is an effective ARB in terms of crossing the blood–brain barrier.[32] In addition, because previous animal studies have shown that ARBs enable endogenous angiotensin II to stimulate neuronal regeneration via activation of AT_2 receptors,[11] we speculated that candesartan treatment might also restore the reduced cerebral NAA level, particularly in DHT patients. However, candesartan treatment for 3 to 4 months did not significantly alter the NAA level. Because NAA was measured in a small area of the brain, only changes in that small area would have been detected. This may have reduced the sensitivity of our ability to detect a change of NAA by candesartan therapy. A longer follow-up study of these patients may be required to demonstrate the potential beneficial effect of ARB on neuronal damage that has already occurred.

Because of the study limitation that the present study was an open one with ARB, a double-blind randomized controlled trial using renin-angiotensin-aldosterone system inhibitors and other antihypertensives of different classes will be necessary to confirm our results under similar levels of BP lowering. The results of this study provide a rationale for a long-term randomized controlled trial using RAS inhibitors for the prevention of stroke and cognitive dysfunction in preidentified DHT patients.

Conclusion

In hypertensive patients, the existence of diabetes is closely associated with advanced brain damage (reduced functional neuronal mass and CVR). ARB partly improved impaired cerebral microcirculation. This might provide an explanation if ARBs are found to have a benefit in improving clinical outcomes. This beneficial effect should be compared with the effect of a different class of antihypertensive with similar levels of BP lowering as a control in the future.

Acknowledgments

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BP Measurement

Determinants of Exaggerated Difference in Morning and Evening Blood Pressure Measured by Self-measured Blood Pressure Monitoring in Medicated Hypertensive Patients: Jichi Morning Hypertension Research (J-MORE) Study

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Background: Morning blood pressure (BP) surge in ambulatory BP monitoring was a risk factor for stroke in our previous study. We studied the determinants of the morning minus evening systolic BP difference (ME difference) in self-measured BP monitoring, as a possible risk factor for stroke in medicated hypertensive patients.

Methods: Nine hundred sixty-nine hypertensive outpatients receiving stable antihypertensive drug treatment were studied using self-measured BP monitoring in the morning and evening.

Results: The ME difference ranged from −37.3 to 53.3 mm Hg (mean 7.9 mm Hg). The highest quartile (Q4) of the ME difference group (>15.0 mm Hg) had older age (68.0 ± 9.8 years *v* 66.2 ± 10.3 years, $P = .01$) and higher prevalence of men (48.3% *v* 39.9%, $P = .02$), regular alcohol drinkers (34.7% *v* 26.0%, $P = .01$) and β-blocker use (26.9% *v* 19.9%, $P = .03$) than the other quartile groups (Q1 to Q3), whereas there was no significant difference in the average of morning and evening (ME average) BP. In logistic regression analysis controlling for ME average and other confounding factors, independent risks for Q4 of ME difference were older age (10 years older: odds ratio [OR] 1.21, $P = .01$, 95% confidence interval (CI) 1.04–1.42), regular alcohol drinker (OR 1.51, $P = .04$, 95% CI 1.01–2.26), and β-blocker use (OR 1.50, $P = .02$, 95% CI 1.06–2.12).

Conclusions: Older age, β-blocker use, and regular alcohol drinking were significant determinants of the exaggerated ME difference in medicated hypertensive patients.

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Key Words: Self-measured blood pressure monitoring, hypertension, morning surge.

Cardiovascular events tend to occur most frequently in the morning.[1] Elevated morning blood pressure (BP) level was shown to be associated with target organ damage, such as left ventricular hypertrophy[2] and microalbuminuria,[3,4] in some cross-sectional studies. The Ohasama study, a prospective study in the northern part of Japan, showed that morning BP measured by self-measured BP monitoring was an independent predictor of future stroke[5] and mortality.[6] Therefore, morning BP level plays an important role in the incidence of cerebrovascular disease; however, clear evidence about the risk of BP surge in the morning has hitherto been lacking.

Recently, we reported that exaggerated morning systolic BP surge (the morning BP [average of 4 to 5 BP readings during the first 2 h after wake-up time] minus the lowest BP [average of 3 BP readings centered on the lowest night-time reading]) evaluated by ambulatory BP monitoring was an independent risk factor for the prevalence of silent cerebral infarcts and the incidence of stroke events independently of the 24-h BP level.[7] Moreover, morning minus evening systolic BP difference (ME difference) from ambulatory BP monitoring was also shown to be an independent predictor of stroke.[8]

Self-measured BP monitoring is a possible substitute

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for ambulatory BP monitoring.[9] In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (JNC7),[10] the self-measured BP level was evaluated as the average of all BPs measured in the morning and in the evening. However, ME difference may have additional clinical usefulness for the management of hypertensive patients, and exaggerated ME difference with high morning BP and low evening BP may be a risk factor for cardiovascular disease even in medicated hypertensive patients with a well-controlled ME average.

In this study, we investigated ME difference as a possible alternative to the morning ambulatory BP surge, and examined its determinants in medicated hypertensive patients.

Methods

Patients

We studied 1027 hypertensive outpatients with stable antihypertensive drug treatment for at least 3 months. They were consecutively recruited from 43 doctors in 32 different clinics and hospitals in Japan.

Smoking was defined as having a current smoking habit. Chronic renal disease was defined as overt proteinuria or elevated serum creatinine level more than 176.8 μmol/L (2.0 mg/dL). Diabetes mellitus was defined as more than 7.0 mmol/L (126 mg/dL) of fasting blood glucose or more than 11.1 mmol/L (200 mg/dL) casual glucose level in patients who were not treated or treated for diabetes mellitus. Glucose intolerance was defined as fasting blood glucose level in the range of 6.1 to 6.9 mmol/L (110 to 125 mg/dL). Hyperlipidemia was defined as more than 5.7 mmol/L (220 mg/dL) total cholesterol level or more than 1.7 mmol/L (150 mg/dL) triglyceride level. Clinical histories of the patients were obtained from interviews by the patient's own doctors.

All of the antihypertensive medications were classified as calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers, diuretics, α-blockers, and others. Patients who were taking verapamil or diltiazem and dihydropyridine calcium channel blocker were classified as taking one CCB; αβ-blocker was classified as β-blocker. The institutional review board of Jichi Medical School approved this study, and informed consent was obtained from all patients.

Study Protocol

Morning and evening BP were measured using commercially available self-measured BP devices of which the accuracy was validated. All of the patients were instructed to measure BP using a cuff oscillometric device on the same upper arm position for 3 days. If the patients were not using their own self-measured BP devices in daily practice, cuff oscillometric semiautomatic devices (UA-631, A&D, Tokyo, Japan)[11] were given to them for this study. Self-measured BP was conducted twice on each occasion in a seated and relaxed position with the arm bare in the morning (within 1 h after waking, before having breakfast and taking medication) and evening (just before going to bed) for 3 consecutive days (total of six measurements). The first measurement was performed after more than 2 min of rest and the second measurement was performed after an interval of more than 30 sec. The patients were asked to document all of the self-measured BP value on the sheet and report them to their own physician.

Morning BP and evening BP were defined as the average of the first and the second self-measured BP values in the morning and in the evening, respectively, for 3 days (total of six BP measurements). The average of the morning and the evening systolic BP (ME average) was calculated. The ME difference was defined as morning systolic BP minus evening systolic BP.

Clinic BP was measured after resting for at least 5 min at two different clinic visits before and after the self-measured BP monitoring period. Clinic BP was defined as the average of the BPs measured at two visits (9 AM to 5 PM). We did not adjust the time of clinic BP measurements at trough time.

Statistical Methods

After excluding the 58 patients, those on night-shift work (25 patients) and incomplete data sets (33 patients), statistical analyses were conducted for 969 patients using the computer software SPSS version 11.0J (SPSS Inc., Chicago, IL). The comparisons of two parameters were performed by the two-tailed nonpaired t test and comparisons of categorical variables were performed by the χ^2 test. One-way analysis of variance (ANOVA) was performed to detect differences among groups, and Tukey's honestly significant differences (HSD) test was used for multiple pairwise comparisons of means among groups. Odds ratio (OR) and the 95% confidence interval (CI) were calculated by multiple logistic regression analysis. A probability value $< .05$ was considered statistically significant.

Results

Patient Characteristics

The age of the total study population ranged from 32 to 95 years (mean ± SD: 66.5 ± 10.2 years) and 407 men and 562 women were enrolled. All of the 969 patients were taking one or more antihypertensive medications: CCB (71.2%), ACEI (27.3%), ARB (31.6%), β-blockers (21.7%), α-blockers (10.6%), diuretics (12.6%), and others. Thirty-three percent of the patients were taking antihypertensive medication in the evening or before going to bed. Hyperlipidemia was observed in 40.9% of patients. Diabetes mellitus or impaired glucose was observed in 15.9% of patients. Regular alcohol drinkers constituted 28.3% of all patients. Current smokers constituted 12.2%. History of cardiovascular events included angina pectoris (8.3%), myocardial infarction (5.6%), and

stroke (7.4%). Chronic renal disease was present in 5.0% of the patients.

BP Control Status

Clinic BP, morning BP, evening BP, and ME average were 143.0 ± 15.6/80.7 ± 10.1 mm Hg, 139.8 ± 14.6/81.7 ± 10.0 mm Hg, 131.8 ± 14.2/75.9 ± 9.8 mm Hg, and 135.8 ± 13.2/78.8 ± 9.3 mm Hg, respectively. Systolic ME average was controlled to less than 135 mm Hg in 472 patients (49.3% of all patients). We considered 140 mm Hg for clinic systolic BP and 135 mm Hg for self-measured systolic BP at home as the cutoff level, according to the JNC7.[10] Well-controlled clinic systolic BP was seen in 422 patients (43.6% of all patients). Masked morning systolic hypertension (clinic systolic BP <140 mm Hg and self-measured systolic BP in the morning ≥135 mm Hg) was present in 218 patients (22.5% of all patients and 51.7% of well-controlled clinic systolic BP patients).

ME Difference

The ME difference ranged from −37.3 to 53.3 mm Hg (mean: 7.9 mm Hg) and the highest quartile (Q4) of ME difference was more than 15.0 mm Hg (n = 240, median: 21.3 mm Hg). Even in the 472 patients (49.3%) with well-controlled systolic ME average (≤135 mm Hg), exaggerated ME difference (>15 mm Hg) was seen in 109 patients (23.1%) (Fig. 1). The ME difference was not correlated with the ME average (r = 0.04, P = .24), although morning BP and evening BP were correlated with ME difference (morning systolic BP: r = 0.43, P < .001; evening systolic BP: r = −0.37, P < .001).

Determinants of Exaggerated ME Difference

We compared the Q4 group of ME difference group with the other three quartile groups (Q1 to Q3) and evaluated the determinants of the exaggerated ME difference (Table 1). The patients in the Q4 group of ME difference were older (68.0 ± 9.8 v 66.2 ± 10.3 years, P = .01) and had a higher prevalence of male gender (48.3% v 39.9%, P = .02), regular alcohol drinkers (drinker) (34.7% v 26.0%, P = .01), and β-blocker users (26.9 v 19.9%, P = .03) than those in the Q1 to Q3 groups. The prevalence of smokers tended to be lower in the Q4 of ME difference patients than that in the Q1 to Q3 patients (9.5% v 13.1%, P = .17). There was no significant difference in the ME average between the two groups (Q4 v Q1 to Q3: 137.2 ± 14.2 v 135.3 ± 12.9 mm Hg for systolic BP, P = .06; 78.8 ± 8.7 v 78.9 ± 9.5 mm Hg for diastolic BP, P = 0.90) (Table 2). There was no significant difference in the prevalence of patients who were taking antihypertensive medication at night or before going to bed between the two groups (Q4 v Q1 to Q3: 32.2% v 33.6%, P = .753).

In multiple logistic regression analysis, the OR (95% CI) for the Q4 of ME difference were 1.21 (1.04–1.42) for age (10-year increase) (P = .013), 1.50 (1.06–2.12) for β-blocker use (P = .02), 1.51 (1.01–2.26) for drinkers (P = .04), and 0.52 (0.31–0.87) for smokers (P = .01) (Table 3).

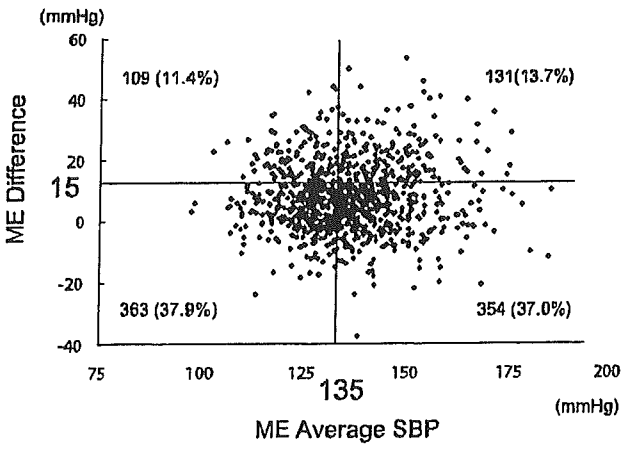

FIG. 1. Prevalence of exaggerated ME difference. ME difference = morning systolic blood pressure (SBP) − evening SBP; ME Average SBP = average of morning SBP and evening SBP.

Regular Alcohol Drinkers

Drinkers had significantly lower evening systolic BP (129.9 ± 14.0 v 132.6 ± 14.2 mm Hg, P = .01) and higher evening heart rate (70.6 ± 10.5 v 67.9 ± 8.6 beats/min, P < .001) than nondrinkers. Morning diastolic BP was significantly higher in drinkers (drinkers versus nondrinkers: 83.6 ± 10 v 81.0 ± 9.9 mm Hg, P < .001), whereas morning systolic BP did not show a significant difference (drinkers versus nondrinkers: 140.1 ± 14.4 v 139.6 ± 14.7 mm Hg, P = .66).

The increase of the ME difference in drinkers was more prominent in elderly patients (aged ≥65 years) than in younger patients (aged <65 years), although ME average was higher in both drinker and nondrinker elderly patients (Fig. 2). The morning systolic BP level was significantly higher in elderly patients than in younger patients in both drinkers and nondrinkers (elderly versus younger patients: 141.2 v 136.9 mm Hg in nondrinkers, P < .001; 142.0 v 137.2 mm Hg in drinkers, P < .01).

Smokers

Smokers had a reduced risk for ME difference in this study. Morning systolic BP (139.7 ± 14.9 v 139.9 ± 12.4 mm Hg, P = .93) and evening systolic BP (131.7 ± 14.2 v 133.0 ± 14.3 mm Hg, P = .34) were not significantly different between nonsmokers and smokers.

Determinants of Morning BP

The patients in the highest quartile of morning systolic BP level (>150 mm Hg) were significantly older (68.9 ± 10.0 v 65.7 ± 10.2 years, P < .001), more used antihypertensive drug classes (1.9 ± 0.9 v 1.7 ± 0.9, P = .01), had a higher prevalence of ACEI use (32.6% v 25.6%, P < .05) and α-blocker use (15.3% v 9.1%, P < .01), had higher clinic systolic BP level (147.6 ± 1.0 v

Table 1. Patient characteristics

	ME Difference		
	The Lower 3 Quartiles (n = 727) (−37.3–14.7 mm Hg)	The Highest Quartile (n = 242) (15–53.3 mm Hg)	P
Age (y)	66.2 ± 10.3	68.0 ± 9.8	.01
Gender (% male)	39.9	48.3	.02
Body mass index (kg/m^2)	24.3 ± 5.0	23.9 ± 3.3	n.s.
Smoker (%)	13.1	9.5	n.s.
Regular alcohol drinker (%)	26.0	34.7	.01
Hyperlipidemia (%)	40.3	42.6	n.s.
Diabetes or IGT (%)	16.6	13.6	n.s.
Chronic renal disease (%)	5.0	5.0	n.s.
Stroke (%)	7.4	7.4	n.s.
Angina pectoris (%)	8.4	7.9	n.s.
Myocardial infarction (%)	5.1	7.0	n.s.
Types of drugs	1.7	1.8	n.s.
Calcium channel blockers (%)	71.0	71.9	n.s.
Short—Intermediate	13.2	9.5	n.s.
Long acting	59.8	62.8	n.s.
β-Blockers (%)	19.9	26.9	.03
ACE Inhibitors (%)	27.5	26.9	n.s.
ARBs (%)	31.2	32.6	n.s.
α-Blockers (%)	10.0	12.4	n.s.
Diuretics (%)	12.5	12.8	n.s.
Nitrates (%)	1.5	1.2	n.s.

Nonpaired t test.
n.s. = not significant ($P \geq .05$); IGT = impaired glucose tolerance;
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

141.5 ± 0.6 mm Hg, $P < .001$) and higher evening systolic BP level (144.6 ± 13.6 v 127.6 ± 11.7 mm Hg, $P < .001$). In multiple logistic regression analysis, the significant determinants for the highest quartile of morning systolic BP level was older age (10-year increase: OR 1.27, 95% CI 1.06–1.52, $P = .01$) and evening systolic BP level (OR: 1.12, 95% CI 1.10–1.14, $P < .001$) after adjustment by use of antihypertensive drug classes, ACEI use, α-blocker use, and clinic systolic BP level.

Discussion

Self-measured BP data were obtained in 969 consecutive hypertensive patients using antihypertensive medication. The

Table 2. Blood pressure and pulse rate

	ME Difference		
	The Lower 3 Quartiles (n = 727) (−37.3–14.7 mm Hg)	The Highest Quartile (n = 242) (15.0–53.3 mm Hg)	P
Clinic SBP (mm Hg)	143.1 ± 15.8	142.8 ± 15.2	n.s.
Clinic DBP (mm Hg)	80.8 ± 10.2	80.3 ± 9.6	n.s.
Clinic PR (/min)	72.9 ± 10.8	71.5 ± 10.0	n.s.
Morning SBP (mm Hg)	136.8 ± 13.2	148.8 ± 15.0	<.001
Morning DBP (mm Hg)	80.6 ± 10.0	85.3 ± 9.3	<.001
Morning PR (/min)	65.6 ± 9.0	64.6 ± 9.2	n.s.
Evening SBP (mm Hg)	133.9 ± 13.6	125.7 ± 14.3	<.001
Evening DBP (mm Hg)	77.0 ± 9.7	72.5 ± 9.1	<.001
Evening PR (/min)	68.4 ± 9.1	69.3 ± 9.6	n.s.
ME Average SBP (mm Hg)	135.3 ± 12.9	137.2 ± 14.2	n.s.
ME Average DBP (mm Hg)	78.8 ± 9.5	78.9 ± 8.7	n.s.
ME Average PR (/min)	67.0 ± 8.6	66.9 ± 8.8	n.s.

Data are shown by mean ± standard deviation.
SBP = systolic blood pressure; DBP = diastolic blood pressure; PR = pulse rate; ME Average = average of morning and evening.

Table 3. Logistic regression analysis for the highest quartile of ME difference

	Model		
	OR	*P*	95% CI
Age (10 y)	1.21	.01	1.04–1.42
Male gender	1.35	.11	0.93–1.97
β-blocker use	1.52	.02	1.06–2.12
Smoking	0.52	.01	0.31–0.87
Regular alcohol drinker	1.51	.04	1.01–2.26
ME Average SBP (10 mm Hg)	1.09	.12	0.98–1.22

OR = odds ratio; ME average SBP = average of morning SBP and evening SBP.
Other abbreviations as in Table 2

ME average in self-measured BP was well controlled (<135 mm Hg) in 49.3% of all patients. The independent determinants for the exaggerated ME difference (>15 mm Hg, 23.1% of the total sample) were older age, regular alcohol drinking, and β-blocker use.

Regular Alcohol Drinking

The prevalence of regular alcohol drinkers was significantly higher in the exaggerated ME difference group (Q4) than in the other ME difference groups (Q1 to Q3). Kawano et al[12] reported that regular alcohol drinking had a biphasic effect on the self-measured BP profile at home (morning BP increase and evening BP decrease). The mechanism by which hypertension is induced by alcohol consumption is unclear; however, possible mechanisms have been reported to include an imbalance of the central nervous system, impairment of the baroreceptors, an increase in sympathetic activity, stimulation of the renin-angiotensin-aldosterone system, an increase in cortisol levels, an increase in intracellular calcium levels with a subsequent increase in vascular reactivity, stimulation of the endothelium to release endothelin or inhibition of endothelium-dependent nitric oxide production, and chronic subclinical withdrawal.[13] Evening alcohol intake at dinner may have contributed to the lower evening BP, and to increased sympathetic activity, which was expressed as increased evening pulse rate. The increased sympathetic activity could contribute to exaggerated morning BP surge, and thus to increase a ME difference.

Some prospective studies[14,15] showed that regular alcohol drinking increases the risk of cerebral bleeding. Heavy alcohol drinking may lead to hypertension with exaggerated morning BP surge and this may be a trigger for cerebral bleeding. On the other hand, regular alcohol drinking increased the risk for exaggerated ME difference in this study, although many prospective studies[16–19] have shown that mild-to-moderate alcohol drinking reduces the risk of cardiovascular disease. The beneficial effect of regular alcohol consumption may be partly explained by factors such as anti-inflammatory and anticoaglatory effects. The C-reactive protein (CRP), a marker of inflammation, is related to atherosclerosis[20] and higher a CRP level is a risk factor for cardiovascular events.[21] In regular alcohol drinkers, the CRP level had been reported to be decreased[22] and alcohol might have some anti-inflammatory effects in the pathogenesis of atherosclerosis. In addition, Mukamal et al[23] reported that mild-to-moderate alcohol consumption was associated with lower coagulability.

β-Blocker Use

In this study, the β-blocker use was found to be a determinant of exaggerated ME difference. Most of the patients were taking antihypertensive drugs once daily in the morning, but the dosage and timing of taking drugs were different among the patients. Antihypertensive drugs changed the effects on the morning BP[24–26] and Morgan and Anderson[27] compared the difference in the time-dependent effects during the day among placebo, felodipine (CCB), hydrochlorothiazide (diuretic), atenolol (β-blocker), and perindopril (ACEI) users. Atenolol did not reduce BP during sleep, and it caused a significantly smaller reduction of morning BP than the other three drugs.

Morning BP is affected by circadian variation of the autonomic nerves. Panza et al[28] measured forearm vascular resistance at three different times of day (7 AM, 2 PM, and 9 PM) and found that the basal forearm vascular resistance was significantly higher and the blood flow was significantly lower in the morning than in the afternoon and evening. The vasodilator effect of phentolamine (an α-adrenergic antagonist) was also most significant in the morning, indicating that there was a α-sympathetic nerve dominant BP increase in the morning. Pickering et al[29] evaluated the effect of a single daily dose of doxazosin (an α-blocker) given at night and found that the greatest reduction of BP occurred in the morning hours. We recently found that the predominant BP reduction in the morning due to doxazosin was associated with the pro-

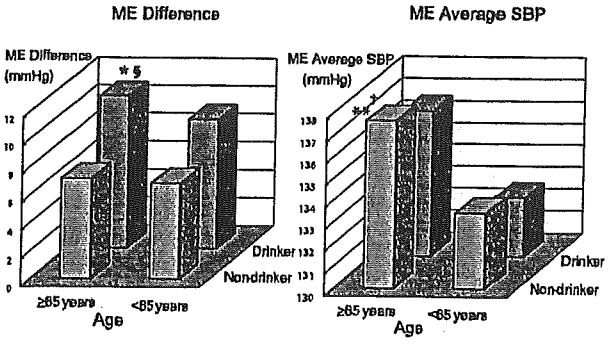

FIG. 2. Impact of age and drinking on ME difference. ME difference = morning systolic blood pressure (SBP) – evening SBP; ME Average SBP = average of morning SBP and evening SBP. *P < .01, **P < .001 *v* age <65 years and nondrinker group; §P < .01 *v* age ≥65 years and nondrinker group; †P < .01 *v* age <65 years and drinker group.

gression of silent hypertensive cerebral disease.[30] Thus, the association between the exaggerated ME difference and β-blocker may be due to the predominant α-sympathetic activation due to β-sympathetic blockade. However, because of the limitations of this study, further prospective evaluations will be needed to evaluate the relationship between β-blockers and exaggerated ME difference.

Age

Older age was also a risk factor for exaggerated ME difference in this study. Morning BP is influenced by α-sympathetic nerve activation.[31] Autonomic nerve function is altered with aging. In the elderly, muscle sympathetic nerve activity has been reported to be increased.[32] Dinenno et al[33] reported that human aging is associated with a reduction in forearm postjunctional α_1-adrenergic responsiveness to endogenous norepinephrine release. In addition, autonomic support of BP changes with aging are due to decreased cardiac vagal inhibition of heart rate and cardiac output and basal sympathetic activity.[34] These imbalances of α_1-sympathetic nerve and β-sympathetic nerve effects may cause increased variability of BP in the elderly.

Baroreceptor sensitivity, a regulator of BP, plays an important role in the regulation of BP and has been reported to be decreased in the elderly.[35] Jones et al[36] showed that aging in men was associated with a marked reduction in baroreceptor buffering of BP and that this was related to increases in basal sympathetic nerve activity and a reduction in systemic α_1-adrenergic vascular responsiveness. In a study of hypertensive patients using direct BP and electrocardiogram monitoring for a 24-h period, the baroreflex sensitivity index (BRI) measured on the basis of the ratio delta RR/delta Ps (delta Ps = spontaneous decrease in systolic BP, delta RR = change in RR) was minimal early in the morning.[37] These data show that impaired baroreceptor sensitivity is a key physiological mechanism of exaggerated ME difference in relation with the predominant α-sympathetic activity in the elderly. Actually in this study, the effect of alcohol on the ME difference was greater in elderly hypertensives than in younger hypertensives.

Smoking

Smoking is a risk factor for cerebrovascular disease. Smoking increases BP and heart rate during the smoking period,[38] although the relationship between smoking and sustained hypertension is controversial.[39] Mann et al[40] reported that smoking is associated with increased daytime BP without causing a change in night-time BP. We expected that smoking would be associated with an increase in ME difference; however, the obtained result was the opposite.

Study Limitations

There is no data that show the prognostic significance of morning minus evening systolic BP difference (ME difference) by self-home BP measurements. In our preliminary analysis, which showed that the ME difference was an independent predictor for stroke, the ME difference was defined by the ambulatory BP data.[8] Because ME difference measured using morning and evening self-home measurements (awake, seated home measurements) may have different prognostic significance from ME difference based on the ambulatory BP data, further studies will be necessary to evaluate the clinical significance of ME difference measured by self-home BP measurements.

The self-measured BP level can be a risk for target organ damage and cerebrovascular events. We showed the determinant of ME difference and how to evaluate self-home BP in treated hypertensive patients.

In addition, ME difference include two types. One is the exaggerated morning BP elevation, and the other is the large evening BP reduction. We were unable to exclude the effect of evening BP reduction (such as regular alcohol drinkers) in exaggerated ME difference. Moreover, the determinants of absolute value of ME difference was almost the same as that of ME difference (morning minus evening BP value).

In conclusion, older age, regular alcohol drinking, and β-blocker use were independent determinants of the risk of exaggerated ME difference in medicated hypertensive patients. Morning BP levels should be monitored in medicated hypertensive patients having these conditions, even if their clinic BP is well controlled.

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Regular Article

Incidence of heparin-PF4 complex antibody formation and heparin-induced thrombocytopenia in acute coronary syndrome

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Abstract A multicenter prospective study on the rate of seroconversion of antibodies to heparin-PF4 complexes (heparin-induced thrombocytopenia [HIT] antibodies) during and after heparin treatment for 4 weeks was carried out in Japanese patients with acute coronary syndrome (ACS). A total of 254 ACS patients treated with heparin were enrolled consecutively from 12 facilities of cardiology. Two patients with preexisting HIT antibodies were excluded from the analysis. The total seroconversion rate for four weeks during and after heparin treatment was 8.7% (n=22, 95% confidence interval [CI]: 5.9–13.1), including values of 3.2% (n=8) at the end of heparin infusion and 5.5% (n=14) at 4 weeks. Among 22 seroconverted patients, four developed HIT and two of the four had the complication of thrombosis. The incidence of HIT was 1.6% (n=4, 95% CI: 0.04–3.1). The risk for thromboembolic development was higher in the seroconverted patients (odds ratio, 17.4, 95% CI: 5.2–58.4, p<0.0001) than nonconverted patients. An analysis of factors affecting the seroconversion rate was carried out. The seroconversion rate for ACS patients who underwent percutaneous coronary intervention (PCI; n=163) was 12.3%, significantly higher than the 2.3% in patients who did not undergo PCI (n=89), leading to an odds ratio of 6.1 (95% CI: 1.4–26.7, p=0.009). A significant odds ratio was obtained for each factor affecting the seroconversion: 3.5 (95% CI: 1.3–9.9, p=0.014) for more than 5 days of heparin infusion, 3.0 (95% CI: 1.2–7.6, p=0.035) for

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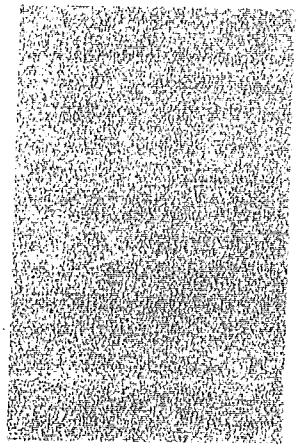

a thrombotic history and 2.7 (95% CI: 1.1–6.8, p=0.039) for hyperlipidemia. No other factor, including age or diabetes mellitus, contributed to the seroconversion. Therefore, PCI, duration of heparin treatment and thrombotic history facilitated the seroconversion in ACS patients. PCI patients treated for more than 5 days with heparin showed a maximal seroconversion rate of 18.3% (95% CI: 13.8–22.2). This high rate in PCI patients did not interact with age, type of underlying disease of unstable angina or myocardial infarction or thrombotic history.

In conclusion, ACS patients demonstrating seroconversion are at risk of thromboembolic development due to the likelihood of immunomediated endothelial dysfunction. The increase in the rate of seroconversion in ACS patients would be affected by factors such as PCI with mechanical stress, longer duration of heparin treatment, thrombotic history and presence of hyperlipidemia. If PCI is undertaken with heparin anticoagulation for more than 5 days, seroconversion would easily occur, and the seroconverted patients could subsequently suffer from HIT.

Introduction

Heparin treatment has been in use in many years, and there is now concern over heparin-induced thrombocytopenia (HIT), an immune-mediated thrombocytopenic disorder and a potentially life-threatening adverse reaction to therapy with heparin. HIT associated with thrombosis (HITT) is frequently complicated by venous and arterial thrombosis and can potentially lead to limb amputation and death in patients with HIT.

The formation of antibodies to heparin-PF4 complexes (HIT antibodies) is thought to be the main causative factor in the development of HIT. Namely, macromolecular immune-complexes of heparin-PF4 and HIT antibodies bind to platelets via their FcγIIA receptor leading to the aggregation of platelets, release of microparticles and hence to the production of thrombin [1]. The incidence of seroconversion in 109 medical patients treated with unfractionated heparin (heparin) was reported to be 17%, and one patient (0.9%) with thrombocytopenia, having a >50% decrease from baseline, was diagnosed with HIT. A follow-up assay of HIT antibodies has been a useful tool for the detection of heparin-treated patients at risk of developing HITT [2]. The rate of seroconversion of HIT-antibodies was higher in patients who underwent cardiopulmonary bypass surgery without developing HIT than those who actually developed HIT. This concept has been depicted in the iceberg model of HIT [3]. The difference in the seroconversion rate between the sources of heparin was studied in 207 patients undergoing cardiac surgery. The rates were 44.4% and 30.6% for bovine and porcine heparin, respectively. It has been suggested that bovine heparin induces seroconversion more than porcine heparin [4]. A follow-up study after the onset of HIT showed that HIT antibodies fell to undetectable levels at a median of 50 to 85 days and did not recover with subsequent reexposure to heparin [5]. In the clinical setting, several subtypes of HIT, including rapid [5], delayed [6] and early-onset [7], have been reported besides the typical onset, often associated with acute systemic reaction and/or thrombotic complications. However, the location of a thrombus has thought to be influenced by atherosclerosis, postoperative state and the mechanical stress of catheter manipulations, and to be superimposed by HIT antibody-induced endothelial damage. Procoagulant activity derived from the damaged endothelium may also contribute to thrombosis [8].

To estimate the incidence of seroconversion in hospitalized patients with acute coronary syndrome (ACS) requiring heparin anticoagulation, a prospective cohort study was conducted. Also, some of the factors facilitating seroconversion in patients with ACS were studied. Percutaneous coronary intervention (PCI) is usually chosen to achieve the revascularization of a narrowed or occluded coronary artery in the clinical setting. This study was also carried out to clarify whether or not PCI promotes seroconversion because PCI induces plaque disruption and platelet activation through mechanical stress and is prone to cause thrombogenesis.

Materials and methods

A total of 254 patients with ACS who had received heparin (unfractionated porcine heparin, Japan pharmacopoeia) at 12 medical facilities of cardiology were enrolled consecutively between May 2001 and May 2002. Informed consent was obtained from each patient. The diagnosis of