Methods

Patients

We studied 400 essential hypertensive patients (mean age, 68 ± 9 years; range, 41 to 88 years; 152 men and 248 women), composed of 161 patients diagnosed with diabetic hypertension (diabetic group) and 239 with nondiabetic hypertension (nondiabetic group). We enrolled hypertensive outpatients into our study from three participating institutes (one clinic, two hospitals). Hypertensive patients were consecutively selected according to the following criteria: 1) essential hypertension with average clinic systolic BP >140 mm Hg or average clinic diastolic BP of >90 mm Hg (average for each patient on two or more occasions) if not medicated;[11] 2) taking antihypertensive medication because of hypertension; and 3) aged ≥40 years old. No patient had taken any antihypertensive medication for at least 1 week before the ambulatory BP monitoring. None of the patients were hospitalized during the study period. We excluded patients with renal failure (serum creatinine ≥132.6 mmol/L), hepatic damage, secondary or malignant hypertension, symptomatic ischemic heart disease or other cardiac disease, congestive heart failure, arrhythmias including atrial fibrillation, stroke (including transient ischemic attacks), or other severe concomitant disease.

Diabetes mellitus was defined according to the criteria of the American Diabetes Association.[12] All of the diabetic patients had type 2 diabetes mellitus. Body mass index (BMI) was calculated as weight (in kilograms)/height (in meters squared). The HbA_{1C} data were calculated as an average of the recent 5 years of HbA_{1C} if there were more than 5 years of data for each patient. If there were less than 5 years of HbA_{1C} data, we used all of the HbA_{1C} data available to calculate the average HbA_{1C}. This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, Jichi, Japan. All of the patients gave informed consent for this study.

Echocardiographic Measurements and Calculation

M-mode echocardiography, guided by a two-dimentional echocardiography, was performed with the patient maintained in a partial left decubitus position.

Echocardiographic tracings were performed by one physician using the same procedure in a blinded manner at all three centers. Standardization of tracing was performed in the same manner at all three institutes. The LV internal dimension, interventricular septal thickness, and posterior wall thickness were measured at end-diastole and end-systole according to the American Society of Echocardiography (ASE) recommendations.[13] When optimal orientation of the M-mode line could not be obtained, correctly oriented leading edge linear dimension measurements were made from two-dimensional images according to ASE recommendations.[14] The measurements were performed within 3 months before the ambulatory BP monitoring and made in a blinded manner.

End-diastolic LV dimensions were used to calculate LV mass using an anatomically validated formula described previously.[15] The LV mass index (LVMI) was calculated for each patient by dividing LV mass by body surface area (BSA). Relative wall thickness (RWT) was calculated as twice the posterior wall thickness divided by the end-diastolic LV dimension. End-diastolic and end-systolic LV volumes were calculated by the Teichholz method. Linear measurement-derived ejection fraction was calculated as the percentage reduction of LV volume from end-diastole to end-systole. The presence of LV hypertrophy (LVH) was defined by sex-specific criteria (LVMI ≥110 g/m^2 in women and ≥134 g/m^2 in men) as described previously.[16]

Reproducibility

Twenty LV mass and RWT measurements were performed by one observer at two separate times for determination of intraobserver variabilities. The results were expressed as a linear regression between the two measurements and as a percent error that was derived as 100 times the absolute difference between measurements divided by the initial measurements. The intraobserver correlation coefficient and the percent error of LV mass was 0.91 and 0.39% ± 12.9%, and that of RWT was 0.92 and 3.99% ± 9.2%, respectively.

24-h Ambulatory BP Monitoring

Noninvasive ambulatory BP monitoring was carried out on a weekday with an automatic system using electric-powered cuff inflation (TM2421, A&D, Tokyo, Japan), which recorded both BP (by the oscillometric method) and pulse rate every 30 min for 24 h. The same ambulatory BP monitoring device was used at the three centers and the data were analyzed by the same method. The accuracy of this device was previously validated. Sleep BP was defined as the average of BP measurements 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 BP measurements recorded during the rest of the day. Nondipper was defined as sleep systolic BP/awake systolic BP ratio >0.90. Sustained hypertension (SHT) and white coat hypertension (WCHT) were defined as follows: clinic BP >140/90 mm Hg (either) and 24-h BP ≥135/80 (either) mm Hg for SHT; clinic BP >140/90 mm Hg (either) and 24-h BP <135/80 mm Hg (both) for WCHT.

Statistical Analysis

All statistical analyses were carried out with SPSS/Windows, version 11.0J (SPSS Inc., Chicago, IL). The χ^2 test was used to calculate proportions (Tables 1 to 4). Unpaired t tests or one-way analysis of variance was performed to detect differences of mean values between the diabetic and nondiabetic group (Tables 1 to 4). Tukey's honestly significant difference test was used for multiple comparisons of variables between two of four groups (WCHT + diabetes, WCHT + nondiabetes, SHT + diabetes, and SHT + nondiabetes) (Table 3).

Table 1. Baseline characteristics of 400 diabetic or nondiabetic patients

	Diabetic Group (n = 161)	Nondiabetic Group (n = 239)	P
Age (years)	67 ± 9	68 ± 9	.09
Male gender (%)	70 (43)	82 (34)	.07
Body Mass Index (kg/m^2)	25 ± 4	24 ± 3	.15
Height (cm)	155 ± 9	153 ± 9	.04
Weight (kg)	59.0 ± 12	56.3 ± 10	.015
Smoker (%)	46 (29)	67 (28)	.9
Hematocrit (%)	40 ± 5	40 ± 4	.1
Duration of hypertension (y)	9 ± 9	7 ± 6	.03
Duration of diabetes (y)	11 ± 8	ND	
Hemoglobin A_{1C} (%)	7.35 ± 1.1	ND	
Total cholesterol (mmol/L)	5.30 ± 0.85	5.35 ± 0.91	.4
Triglyceride (mmol/L)	1.61 ± 0.86	1.34 ± 0.60	.001
Serum creatinine (mmol/L)	70.7 ± 35.4	70.7 ± 17.7	.2
Clinic SBP (mm Hg)	155 ± 17	164 ± 16	<.001
Clinic DBP (mm Hg)	82 ± 10	89 ± 12	<.001
24-h SBP (mm Hg)	144 ± 17	144 ± 15	.8
24-h DBP (mm Hg)	80 ± 9	82 ± 9	.04
24-h PR (beats/min)	70 ± 9	67 ± 8	.002
Awake SBP (mm Hg)	149 ± 17	151 ± 15	.4
Awake DBP (mm Hg)	83 ± 9	86 ± 10	.01
Awake PR (beats/min)	74 ± 9	71 ± 9	.01
Sleep SBP (mm Hg)	135 ± 19	132 ± 17	.08
Sleep DBP (mm Hg)	74 ± 10	75 ± 10	.4
Sleep PR (beats/min)	63 ± 9	60 ± 8	<.001
Sleep:awake BP ratio	0.91 ± 0.1	0.88 ± 0.1	<.001
Nondipper (%)	86 (53)	102 (43)	.04

Data are number (%) or mean ± SD. Overall P values are shown for two-group comparison of means (unpaired t test) or percentages (χ^2 test).

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; PR = pulse rate, ND = No data.

Spearman's correlation was used for bivariate analyses between 24-h systolic BP and LVMI and RWT, and between LVMI and RWT. Odds ratios (OR) with 95% confidence intervals (CI) for no or some LVH (0 = those with no LVH; 1 = those with LVH criteria) and for RWT (0 = those with RWT <0.45; 1 = those with RWT ≥0.45) were calculated using multiple logistic regression analysis using the following selected independent variables for cardiovascular risk: age, gender (0 = women, 1 = men), BMI, duration of hypertension, smoking (0 = absent, 1 = present), presence of diabetes (0 = absent, 1 = present), 24-h systolic BP, serum creatinine, total cholesterol, and use of antihypertensive med-

Table 2. Comparison of echocardiographic parameters between diabetic and nondiabetic patients

	Diabetic Group (n = 161)	Nondiabetic Group (n = 239)	P
LV mass index (g/m^2)	129 ± 35	130 ± 34	.7
LV mass / height$^{2.7}$	61.4 ± 17	64.1 ± 19	.166
Relative wall thickness	0.50 ± 0.1	0.44 ± 0.1	<.001
Interventricular septal thickness (mm)	10.9 ± 1.5	10.3 ± 1.8	<.001
Posterior wall thickness (mm)	10.9 ± 1.5	10.2 ± 1.6	<.001
LV internal dimension at end-diastole (mm)	44 ± 6	47 ± 5	.03
LV internal dimension at end-systole (mm)	28 ± 5	29 ± 5	<.001
Ejection fraction (%)	72 ± 7	75 ± 6	<.001
Geometric pattern			
Normal pattern (%)	26 (16)	60 (25)	.04
Concentric remodeling (%)	46 (29)	29 (12)	<.001
Concentric hypertrophy (%)	63 (39)	64 (27)	.01
Eccentric hypertrophy (%)	26 (16)	86 (36)	<.001

Data are number (%) or mean ± SD. Overall P values are shown for two-group comparison of means (unpaired t test) or percentages (χ^2 test).

Table 3. Comparison of RWT and LVMI between diabetic and nondiabetic patients

	White Coat Hypertension		Sustained Hypertension	
	Diabetic Group	Nondiabetic Group	Diabetic Group	Nondiabetic Group
n	44	71	117	168
Age (y)	66 ± 9	68 ± 9	67 ± 9	69 ± 9
Male gender (%)	43	35	44	34
LVIDd (mm)	44 ± 6*	47 ± 5	44 ± 6†	47 ± 5
IVS (mm)	10.4 ± 1.2	10.0 ± 1.7	11.1 ± 1.6†	10.4 ± 1.9
PWT (mm)	10.3 ± 1.3	9.9 ± 1.5	11.1 ± 1.5†	10.4 ± 1.7
24-hr systolic BP (mm Hg)	126 ± 7	127 ± 6	151 ± 14	151 ± 11
LV mass index (g/m^2)	118 ± 31	124 ± 31	133 ± 36	132 ± 36
LV mass/height$^{2.7}$	55.2 ± 15	60.4 ± 15	63.8 ± 18§	65.6 ± 21§
Relative wall thickness (%)	0.47 ± 0.1*	0.42 ± 0.1	0.51 ± 0.1‡	0.45 ± 0.1
	12 (27)	13 (18)	52 (44)*	52 (30)

LVIDd = LV internal dimension at end-diastole; IVS = interventricular septal thickness; PWT = posterior wall thickness.
Data are number (%) or mean ± SD.
* $P < .05$, † $P < .01$, ‡ $P < .001$ *v* nondiabetic group; § $P < .05$ *v* diabetic white coat hypertension.

ications (0 = absent, 1 = present). A two-sided P value < .05 was considered statistically significant.

Results

Clinical Characteristics of the Patients

The mean ± SD clinic BP of the overall study group was 157 ± 20 mm Hg systolic and 85 ± 13 mm Hg diastolic, and 24-h BP was 142 ± 16 mm Hg systolic and 80 ± 9 mm Hg diastolic. The prevalence of LVH was 56% and that of RWT ≥0.45 was 50% in the overall study group.

Table 1 shows the characteristics of the 400 hypertensive patients separated into the diabetic group (n =161) and nondiabetic group (n = 239). The age, gender, BMI, smoker, hematocrit, total cholesterol, serum creatinine, and 24-h systolic BP were similar between the groups. However, duration of hypertension, triglycerides, 24-h pulse rates, and sleep/awake BP ratio were significantly higher in the diabetic group than in the nondiabetic group. The clinic systolic BP/diastolic BP, 24-h diastolic BP, and awake diastolic BP were significantly lower in the diabetic group than in the nondiabetic group.

Table 4. Comparison of taking antihypertensives, insulin, and oral hypoglycemics

	Diabetic Group (n = 161)	Nondiabetic Group (n = 239)	*P*
% Taking antihypertensives	121 (75)	168 (70)	.307
Calcium channel blockers	80 (50)	119 (50)	1.000
ACE inhibitors	50 (31)	32 (13)	<.001
Angiotensin 1 receptor blockers	41 (25)	23 (10)	<.001
Diuretics	32 (20)	24 (10)	.008
β blockers	9 (6)	10 (4)	.633
α_1 blockers	5 (3)	1 (0)	.041
Numbers taking antihypertensives	1.4 ± 1.0	0.9 ± 0.8	<.001
% Taking insulin	45 (28)	0	<.001
% Taking oral hypoglycemics	102 (63)	0	<.001
% Taking sulfonylureas	62 (39)	0	<.001
% Taking metformin	33 (20)	0	<.001
% Taking α-glucosidase inhibitors	48 (30)	0	<.001
% Taking aldose reductase inhibitor	14 (9.0)	0	<.001
% Taking pioglitazone	4 (2.5)	0	.026
Numbers taking oral hypoglycemics			
0	44 (27)	0	<.001
1	49 (30)	0	<.001
2	47 (29)	0	<.001
3	21 (13)	0	<.001

Data are number (%) or mean ± SD. Overall *P* values for two-group comparison of means (unpaired *t* test) or percentages (χ^2 test).

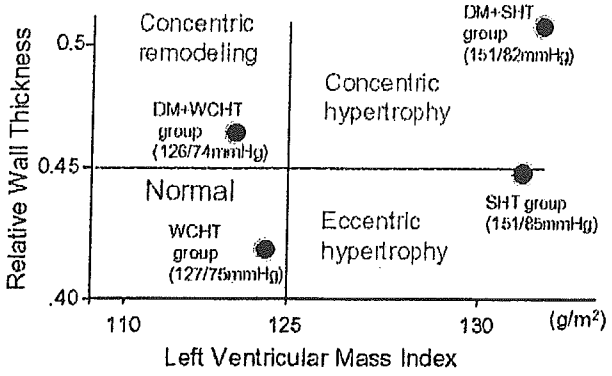

FIG. 1 Characteristics of the LV geometric remodeling pattern in each group. The average values of left ventricular mass index and relative wall thickness were plotted for each group. SHT = sustained hypertension (24-h systolic BP ≥135 mm Hg); WCHT = white coat hypertension (24-h systolic BP <135 mm Hg); DM = diabetes mellitus. Each average 24-h BP value is indicated between parentheses.

LV Mass and LV Geometry

As shown in Table 2, LVMI and LV mass/height$^{2.7}$ were similar between the diabetic group and nondiabetic group, but RWT was significantly higher in the diabetic group than in the nondiabetic group. Twenty-four-hour BP was significantly associated with LVMI and RWT in both the diabetic group ($r = 0.33$, $P < .001$) and nondiabetic group ($r = 0.23$, $P < .001$). There were significant positive relationships between LVMI and RWT in the nondiabetic group ($r = 0.27$, $P < .001$), but no relationship was found in the diabetic group ($r = 0.05$, $P = .51$). In our population, there were only 10 patients with a BMI more than 30 kg/m^2 in the diabetic group (6.2%) and only 8 in the nondiabetic group (3.3%). Therefore, LV mass corrected by BSA would not underestimate the deviation from normal due to body size variation within the two groups.

As shown in Table 3, age, gender, 24-h BP, and LV mass were not significantly different between the diabetic group and nondiabetic group within the same group of WCHT or SHT. The RWT was greater in the diabetic group than in the nondiabetic group. Although the prevalence of concentric LV hypertrophy was higher in the diabetic group than in the nondiabetic group only in the SHT group, it was not different between the WCHT and SHT groups within the diabetic group or nondiabetic group. We plotted the mean value of LVMI and RWT in each of the four groups and showed that 24-h systolic BP was associated with LVMI and presence of diabetes was associated with RWT (Fig. 1).

Table 4 shows the antihypertensive medication status and antidiabetic drugs used in this study. Although there were no significant differences in the rate of antihypertensive medication, the percentage taking angiotensin-converting enzyme (ACE) inhibitors, angiotensin type 1 receptor blockers (ARBs), and diuretics was significantly higher among diabetics than among nondiabetics.

By multiple logistic regression analysis, LVH was only associated with 24-h BP. However, higher RWT (≥0.45) was associated both with presence of diabetes and 24-h systolic BP (Table 5). To assess the effect of antihypertensive medication, we added antihypertensive medication status (0 = absent, 1 = present at examination), calcium channel blockers (CCBs), ACE inhibitors, ARBs, and diuretics (0 = absent, 1 = present before examination) to the model shown in Table 5, but the results were not significantly changed and only ACE inhibitor use was associated with relative wall thickness.

Discussion

In this cross-sectional study, we examined the impact of diabetes and ambulatory BP on LV structure in hypertensive patients. We found associations of type 2 diabetes with higher RWT and higher prevalence of concentric hypertrophy independent of ambulatory BP. In contrast to

Table 5. Determinants of LV hypertrophy and relative wall thickness ≥0.45 in overall patients

	Presence of LV Hypertrophy	Relative Wall Thickness ≥0.45
Age (10 y)	1.27 (0.99–1.64)	1.39 (1.06–1.81)*
Male gender	0.75 (0.46–1.21)	2.02 (1.23–3.32)†
Body mass index (kg/m^2)	1.04 (0.98–1.11)	1.02 (0.95–1.08)
Presence of diabetes	0.69 (0.44–1.09)	2.76 (1.73–4.41)†
24-h SBP (10 mm Hg)	1.32 (1.14–1.52)*	1.17 (1.01–1.37)*
Cholesterol (mg/dL)	1.00 (0.99–1.01)	1.00 (1.00–1.01)
Creatinine (mg/dL)	1.42 (0.65–3.14)	0.86 (0.43–1.74)
CCBs	0.74 (0.48–1.14)	0.96 (0.61–1.49)
ACE inhibitors	1.43 (0.81–2.53)	2.43 (1.35–4.38)†
ARBs	1.24 (0.66–2.34)	1.34 (0.70–2.53)
Diuretics	1.15 (0.59–2.22)	1.76 (0.89–3.50)

Data are shown as odds ratio (95% confidence interval).
SBP = systolic BP; CCB = calcium channel blocker; ACE = angiotensin-converting enzyme; ARB = angiotensin type 1 receptor blocker. Gender was coded as male = 1, female = 0; antihypertensive drugs were coded as 1 = present, 0 = absent.
* $P < .05$, † $P < .001$.

the findings of previous reports,[4,5] LVMI was not increased in the diabetic group compared to the nondiabetic group. There was an association between treatment with ACE inhibitors and concentric LV geometry, possibly because there was a significantly higher percentage of ACE inhibitor users among diabetics. Echocardiographically determined LV mass and geometry are clinically important to stratify the risk in essential hypertension.[17] In a recent study, oxygen utilization of myocardium was lowered in concentric hypertrophy,[18] and concentric hypertrophy has been identified as having the worst cardiovascular prognosis.[6–8]

The reason LV mass did not differ between the diabetic group and nondiabetic group may be because there were no significant differences in BMI between the groups. Obesity, along with insulin resistance, directly promotes myocardial hypertrophy and is a strong determinant of LVH.[19–21] In our population, average BMI was similar between the diabetic group and nondiabetic group. This may also contribute to explaining the fact that diabetic patients did not have larger LV internal diameter as compared to nondiabetic hypertensive subjects. Therefore, our population was appropriate for analysis of the association of LV mass and LV geometric remodeling independent of BMI. Ethnicity can be a contributing factor to explaining the differences in the cardiovascular phenotype.[22] In many previous reports, BMI in Japanese or Chinese diabetic patients was relatively lower than that in Western populations.[23–25] The pathogenesis of diabetes in an Asian population might be completely different from that in an American diabetic population.

In the present study, although diabetic patients clearly had thicker cardiac walls (11 *v* 10 mm), they did not have an increased cardiac mass (129 *v* 130 mg/m^2) because their chambers were less dilated than those of nondiabetic patients (44 *v* 47 mm). After controlling for body height, LV dimension in diabetics was still significantly smaller. In previous reports, there were conflicting results about LV dimension in diabetic patients. In the report by Palmieri et al[4] there were no differences in LV end-diastolic dimension between diabetics and nondiabetics. On the other hand, LV end-diastolic dimension in diabetics was smaller than that in controls.[26,27]

Hypertension is the most powerful determinant of LVH. In the present study, SHT with diabetes showed the greatest RWT and prevalence of concentric hypertrophy, compared with SHT without diabetes or WCHT with diabetes. Higher ambulatory BP was a great contributor to increased LV mass, even in the diabetics. We propose the following two mechanisms: 1) LVH in diabetes depends primarily on connective tissue deposition, whereas hypertension has a greater effect on cardiocyte size.[28] 2) Duration of hypertension and higher peripheral resistance might play an important role in the development of concentric hypertrophy. In the Framingham study, the determinants of concentric hypertrophy were greater severity of hypertension, advancing age, and higher peripheral resistance with normal intravascular volume.[29] In the present study, duration of hypertension was significantly greater in the diabetic group. Sympathetic nervous activation associated with insulin resistance of diabetes[20] or glucose resistance[30] might play an important role in higher peripheral vascular resistance.

The discontinuation of antihypertensive therapy might have been insufficient for ambulatory BP monitoring. However, we discontinued antihypertensive drugs for at least 1 week in all nondiabetics and most diabetics except for supposed high-risk individuals taking multiple antihypertensive drugs or having diabetic microvascular complications. Therefore, we considered the ambulatory BP values in the present study to be nearly valid ambulatory BP data. Ethically, we could not stop antihypertensive drugs for more than 1 week in high-risk individuals, and this might be a limitation of the study.

In conclusion, in a sample of Japanese hypertensive subjects, type 2 diabetes was associated with concentric LV geometry independent of ambulatory BP. In relatively lean body, diabetic hypertensive patients, LV remodeling already begins in the silent stage, which implies a high risk of future cardiovascular disease.

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Short- and Long-Term Incidence of Stroke in White-Coat Hypertension

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Abstract—White-coat hypertension (WCH) has been associated with a low risk for stroke, but long-term data are scanty. We analyzed individual data from 4 prospective cohort studies from the United States, Italy, and Japan that used comparable methodology for 24-hour noninvasive ambulatory blood pressure monitoring (ABPM). Overall, 4406 subjects with essential hypertension and 1549 healthy normotensive controls who were untreated at the time of initial ABPM were followed for a median of 5.4 years up to censoring or occurrence of a first stroke. At entry, mean age of subjects was 56 years (range 18 to 97). Prevalence of WCH was 9%. During follow-up, there were 213 new cases of stroke. Stroke rate (×100 person years) was 0.35 in the normotensive group, 0.59 in the WCH group, and 0.65 in the group with ambulatory hypertension. In a multivariate analysis, the adjusted hazard ratio for stroke was 1.15 (95% confidence interval [CI], 0.61 to 2.16) in the WCH group (P=0.66) and 2.01 (95% CI, 1.31 to 3.08) in the ambulatory hypertension group (P=0.001) compared with the normotensive group. After the sixth year of follow-up, the incidence of stroke tended to increase in the WCH group, and the corresponding hazard curve crossed that of the ambulatory hypertension group by the ninth year of follow-up. In conclusion, WCH was not associated with a definitely increased risk of stroke during the total follow-up period. However, WCH might not be a benign condition for stroke in the long term. (***Hypertension*. 2005;45:203-208.**)

Key Words: blood pressure monitoring, ambulatory ■ stroke ■ blood pressure

White-coat hypertension (WCH),[1] referred to as office[2] or isolated clinic[3] hypertension, is defined by a persistently elevated clinic blood pressure (BP), with normal BP outside the hospital or doctor's office.[1–4] The prognostic significance of WCH is emerging from some event-based cohort[5–8] and interventional[9] studies, which suggest that individuals with WCH have a risk of major cardiovascular events apparently comparable with that of clinically normotensive subjects and markedly less than that of subjects with elevated daytime BP.

Almost all these studies examined a composite pool of cardiovascular events, so that any specific association between WCH and cerebrovascular or coronary events remains elusive. In a study from Japan,[6] incidence of stroke was comparable between clinically normotensive individuals and subjects with WCH and increased in subjects with higher levels of ambulatory BP.[6] However, conclusions of this study are hardly applicable to different ethnic groups at lower stroke risk.

In the present study, we pooled and analyzed individual data from 4 prospective cohort studies from the United States, Italy, and Japan that used comparable methods for 24-hour noninvasive ambulatory BP monitoring (ABPM).

Methods

The International Collaborative Study of the Prognostic Utility of ABPM was initiated to examine the relationship between ambulatory BP and the risks of cardiovascular disease using individual data from a pooled sample of large observational cohorts that contain ambulatory BP measurements. The aims of the study, the structure of the database, and all analytic and publication aspects were discussed and agreed on in advance. The study from the United States was the New York Prognostic Effects of ABPM (NYPEAP)[10]; the study from Italy was the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA)[5,11]; and the studies from Japan were the Ohasama study[12] and the Jichi Medical School (JMS)-ABPM Study, Wave 1.[6,13] Details regarding inclusion and exclusion criteria in the single studies have been published previously.[5,6,10–13]

The majority of subjects in the NYPEAP (83%), PIUMA (88%), and JMS-ABPM (88%) cohorts had a clinic BP ≥140 mm Hg systolic BP (SBP) or 90 mm Hg diastolic BP (DBP) at entry compared with only 27% in the Ohasama community sample. Subjects on antihypertensive medications in NYPEAP, PIUMA, and Tochigi, but not Ohasama, were withdrawn from medications for a minimum of 2 weeks before ABPM. In NYPEAP, PIUMA, and JMS-ABPM, clinically normotensive subjects (ie, those with office BP <140 mm Hg SBP and 90 mm Hg DBP) were generally healthy volunteers recruited from the hospital staff or asymptomatic subjects without medical problems referred to the hospital facility for various reasons.

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Subjects with overt cardiac or cerebrovascular disease, cancer, or hepatic or renal disease at enrollment were excluded. Subjects with diabetes, defined by a fasting glucose of 7.8 mmol/L or use of an oral hypoglycemic agent or insulin, were included. All subjects provided informed consent to be included in each of the 4 studies, which were approved by local ethical committees.

BP Measurement

Details regarding the procedures for clinic BP and ABPM in the NYPEAP,[10] PIUMA,[5,11] Ohasama,[12] and JMS-ABPM[6,13] cohorts have been published previously. Clinic BP was taken at the time of enrollment into the study. In the NYPEAP study, a BP taken by the physician was available for 85% of participants. When missing, the clinic BP taken by a nurse was substituted.

In all 4 studies, ABPM was carried out at entry. In the PIUMA study, the monitor (SpaceLabs 5200, 90202, or 90207; SpaceLabs) was set to measure BP every 15 minutes during the entire 24-hour period. In the NYPEAP study, readings were taken either: (1) every 15 minutes between 6 AM and 12 PM and at 30-minute intervals between 12 PM and 6 AM using either a Del Mar Avionics P2 or P3 or a SpaceLabs 5200 (first 672 subjects); or (2) every 15 minutes between 8 AM and 10 PM and at 30-minute intervals between 10 PM and 8 AM using a SpaceLabs 90202 monitor (last 341 subjects).

In the Ohasama study, readings were taken at 30-minute intervals. Well-trained public health nurses visited each participant on a weekday morning to attach the ABPM device and to detach it the next morning. The participants kept a diary to record daily activities. Ambulatory BP was monitored using the ABPM-630 (Nippon Colin), preset to measure BP every 30 minutes. In the JMS-ABPM, noninvasive ABPM was performed on a weekday with 1 of 3 automatic devices (ABPM-630; Nippon Colin; TM-2421 or TM-2425, A&D Co., Inc.), which recorded BP and pulse rate every 30 minutes for 24 hours.

Using self-reports of the times participants went to sleep and woke up, ambulatory BP readings were aggregated to create a mean of all readings taken while awake and the mean of all readings taken during sleep. This was done separately for SBP and DBP and for pulse pressure (PP), the difference between SBP and DBP.

White-Coat Hypertension

WCH was defined by an average awake ambulatory BP <130 mm Hg SBP and 80 mm Hg DBP. We also determined the risk of stroke associated with a definition of WCH based on an awake ambulatory BP <135/85 mm Hg.[14,15]

Follow-Up

Follow-up was based on telephone contacts or periodical clinical visits at the referring facility or through the Regional Stroke Registration System. Stroke was defined as a focal central nervous system lesion considered vascular in origin and having clinical sequelae lasting ≥24 hours. Fatal and nonfatal strokes were included. Transient ischemic attacks were excluded from the present analysis.

Data Analysis

Statistical analysis was performed using SPSS (SPSS) and SAS-Stat (SAS Institute). One-way ANOVA and multiple comparisons with the Tukey test when appropriate were performed to compare the study sites and the 3 groups with clinical normotension, WCH, and ambulatory hypertension. We report the number of strokes that were recorded in each study, the total number of person years of follow-up for that event, and the unadjusted incidence rate. For survival analyses, event-free curves were estimated using Kaplan–Meier product-limit method and compared by the Mantel (log-rank) test. For subjects who experienced multiple events, analysis was restricted to the first event. The independent effect of several prognostic factors on survival was tested by stepwise Cox model.[16]

TABLE 1. Main Characteristics in the Study Population

Variable	Total Cohort (n=5955)	NYPEAP (n=1296)	PIUMA (n=2620)	Ohasama (n=1277)	JMS-ABPM (n=762)	Overall *P*-Value
Age, years	56 (14)	50 (13)	51 (12)	61 (10)	72 (10)	*P*<0.0001
Ethnicity						*P*<0.0001
White, %	64.1	92.2	100	0	0	
Black, %	1.4	6.4	0	0	0	
Asian, %	34.2	0	0	100	100	
Other, %	0.3	1.4	0	0	0	
Sex, % men	50	65	53	34	38	-
Weight, kg	68.2 (16)	75.1 (14)	75.1 (14)	54.0 (9)	56 (10)	*P*<0.0001
Body mass index, kg/m^2	25.3 (3.8)	25.1 (3.5)	26.8 (3.9)	23.4 (3.0)	24.0 (3.5)	*P*<0.0001
Diabetes, %	11.0	not available	7.6	17.5	11.9	-
Cigarette smoking, %	19.7	10.7	23.6	19.3	20.9	-
Total cholesterol, mmol/L	5.43 (1.08)	5.85 (1.11)	5.54 (1.09)	4.98 (0.93)	5.17 (0.88)	*P*<0.0001
Serum creatinine, mmol/L	87.5 (22)	95.5 (23)	87.5 (21)	not available	79.6 (19)	*P*<0.0001
Serum glucose, mmol/L	5.50 (1.35)	5.81 (1.18)	5.63 (1.38)	not available	5.33 (1.39)	*P*<0.0001
Office SBP, mm Hg	149 (23)	150 (21)	154 (20)	131 (18)	160 (22)	*P*<0.0001
Office DBP, mm Hg	90 (14)	94 (11)	95 (11)	74 (11)	91 (14)	*P*<0.0001
Office PP, mm Hg	59 (17)	56 (18)	58 (17)	57 (14)	69 (16)	*P*<0.0001
Awake SBP, mm Hg	139 (17)	141 (17)	141 (16)	129 (14)	145 (18)	*P*<0.0001
Awake DBP, mm Hg	87 (15)	91 (10)	91 (11)	76 (8)	82 (29)	*P*<0.0001
Awake PP, mm Hg	52 (15)	49 (13)	50 (11)	53 (8)	62 (29)	*P*<0.0001
Sleep SBP, mm Hg	121 (18)	122 (18)	124 (17)	112 (15)	127 (18)	*P*<0.0001
Sleep DBP, mm Hg	72 (11)	76 (11)	75 (11)	64 (8)	72 (11)	*P*<0.0001
Sleep PP, mm Hg	49 (11)	46 (13)	49 (11)	48 (8)	55 (11)	*P*<0.0001

TABLE 2. Main Characteristics in the Normotensive Group and in the Groups With WCH and Ambulatory Hypertension

Variable	Normotensive Group (n=1549)	WCH (n=398)	Ambulatory Hypertension (n=4008)	Overall P-Value
Age, years	55 (14)	61 (14)*†	55 (14)	0.0001
Sex, % women	60	63†	45	0.0001
Weight, kg	60.7 (15)†	63.2 (14)*†	71.5 (15)	0.0001
Body mass index, kg/m^2	24.1 (3.4)†	24.9 (3.8)*†	25.9 (3.9)	0.0001
Diabetes, %	14.3†	11.7*†	9.5	0.0001
Cigarette smoking, %	19.9	13.9*†	20.2	0.010
Total cholesterol, mmol/L	5.11 (1.01)†	5.42 (1.07)*‡	5.55 (1.08)	0.0001
Serum creatinine, mmol/L	86.0 (19)	82.4 (17)†	87.6 (23)	0.001
Serum glucose, mmol/L	5.59 (1.40)	5.42 (1.12)	5.50 (1.36)	0.23
Office SBP, mm Hg	124 (11)†	150 (12)*†	158 (19)	0.0001
Office DBP, mm Hg	74 (9)†	86 (11)*†	96 (11)	0.0001
Office PP, mm Hg	50 (10)†	65 (16)*‡	62 (18)	0.0001
Awake SBP, mm Hg	126 (12)†	121 (6)*†	146 (15)	0.0001
Awake DBP, mm Hg	78 (21)†	73 (5)*†	92 (10)	0.0001
Awake PP, mm Hg	48(20)†	49 (6)†	54 (12)	0.0001
Sleep SBP, mm Hg	110 (13)†	110 (11)†	127 (17)	0.0001
Sleep DBP, mm Hg	64 (9)†	63 (7)†	76 (11)	0.0001
Sleep PP, mm Hg	45 (8)†	47 (8)†	51 (12)	0.0001

*$P<0.01$ vs normotensive group; †$P<0.01$ vs ambulatory hypertension; ‡$P<0.05$ vs ambulatory hypertension.

Analyses were stratified by study site because of expected differences in stroke rate between the different groups. Several potential confounding variables assessed at entry were considered in the analysis: current smoking status, weight, height, body mass index, total cholesterol, and use of antihypertensive medication, including those titrated off before ABPM. In 2-tailed tests, P values <0.05 were considered statistically significant.

Results

Cohort Features

As shown in Table 1, age of the subjects was higher in the JMS-ABPM cohort than in the other cohorts (all $P<0.01$). Diabetes was more frequent in the Ohasama sample ($P<0.001$) compared with each of the others, but information was not available from the NYPEAP cohort. Office SBP and PP were highest in the JMS-ABPM cohort ($P<0.01$ versus the other cohorts), whereas office DBP was highest in the PIUMA cohort ($P<0.01$ versus the other cohorts). Comparable differences between the cohorts were found for awake and asleep ambulatory BP.

Differences Between Groups

Age of the subjects (Table 2) was higher in the WCH group than in the other groups. Subjects with WCH tended to be women more frequently, smokers less frequently, and diabetics more frequently when compared with those with ambulatory hypertension (all $P<0.01$). In the WCH group, office BP was intermediate between the normotensive group and that with ambulatory hypertension. In contrast, awake SBP and DBP were lower in the group with WCH than in the normotensive group (both $P<0.01$), whereas sleep SBP and DBP were comparable between the 2 group. Prevalence of subjects treated with antihypertensive drugs resulting from the last telephone contact or clinical visit during follow-up is reported in Figure 1. A similar proportion of subjects included in the normotensive control group or the WCH group at entry were receiving the 5 classes of antihypertensive drugs (all $P<$NS). In contrast, a greater proportion of subjects belonging to the AH group were receiving diuretics, β-blockers, angiotensin-converting enzyme inhibitors or calcium antagonists ($P<0.01$ versus each of the other groups). Frequency of treatment with angiotensin II antagonists did not differ between the groups.

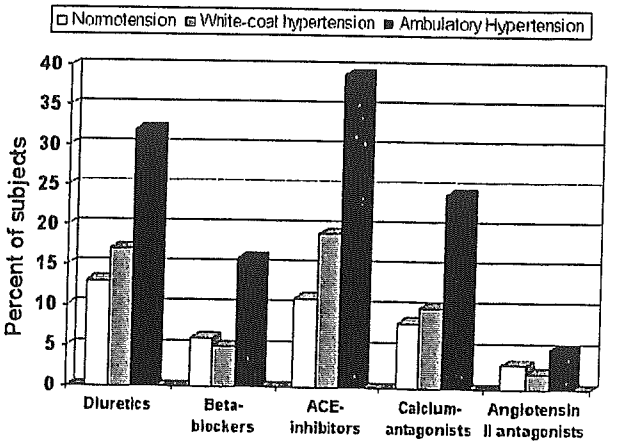

Figure 1. Percentage of subjects treated with antihypertensive drugs resulting from the last telephone contact or clinical visit during follow-up. ACE indicates angiotensin-converting enzyme.

TABLE 3. Entry Characteristics of Subjects With and Without Future Stroke

Variable	No Future Stroke (n=5742)	Future Stroke (n=213)	*P*-Value
Age, years	55 (14)	68 (12)	0.0001
Sex, % men	49.3	56.3	0.04
Weight, kg	68 (16)	64 (16)	0.0001
Body mass index, kg/m^2	25.3 (3.8)	25.0 (4.0)	0.19
Diabetes, %	10.5	23.5	0.0001
Asian ethnic group, %	33.5	53.5	0.0001
Cigarette smoking, %	19.3	29.7	0.0001
Total cholesterol, mmol/L	5.43 (1.08)	5.35 (1.06)	0.293
Serum creatinine, mmol/L	86.9 (22)	91.1 (20)	0.028
Serum glucose, mmol/L	5.50 (1.3)	5.78 (1.8)	0.021
Office SBP, mm Hg	148 (22)	159 (24)	0.0001
Office DBP, mm Hg	90 (14)	90 (14)	0.95
Office PP, mm Hg	59 (16)	69 (19)	0.0001
Awake SBP, mm Hg	139 (17)	149 (19)	0.0001
Awake DBP, mm Hg	87 (15)	87 (12)	0.657
Awake PP, mm Hg	52 (15)	61 (14)	0.0001
Sleep SBP, mm Hg	121 (17)	134 (21)	0.0001
Sleep DBP, mm Hg	72 (11)	76 (12)	0.0001
Sleep PP, mm Hg	49 (11)	58 (14)	0.0001

Incidence of Stroke

There were 213 new cases of stroke. Overall, the JMS-ABPM cohort showed the highest rate of stroke (6.09×100 person years) followed by the Ohasama cohort (2.12×100 person years), the PIUMA cohort (0.59×100 person years), and the NYPEAP cohort (0.19×100 person years).

At entry (Table 3), subjects with future stroke were older, leaner, and more frequently smokers, diabetics, and of Asian ethnic origin than the subjects without future stroke (all $P<0.01$). Office and awake SBP and PP, but not DBP, were higher in the group with future stroke than in that without future stroke (all $P<0.001$). Sleep SBP, DBP, and PP were higher in the group with future stroke (all $P<0.001$).

The cumulative hazard for stroke (Figure 2) differed between the normotensive group, the group with WCH, and the group with ambulatory hypertension (log-rank test; P value for trend=0.0013). Figure 2 shows that the cumulative hazard for stroke was comparable in the WCH and normotensive groups up to the sixth year of follow-up. However, subsequently, there was an increase in the hazard of stroke in the WCH group, with the corresponding curve diverging from that of the normotensive group and crossing that of the ambulatory hypertension group by the ninth year of follow-up.

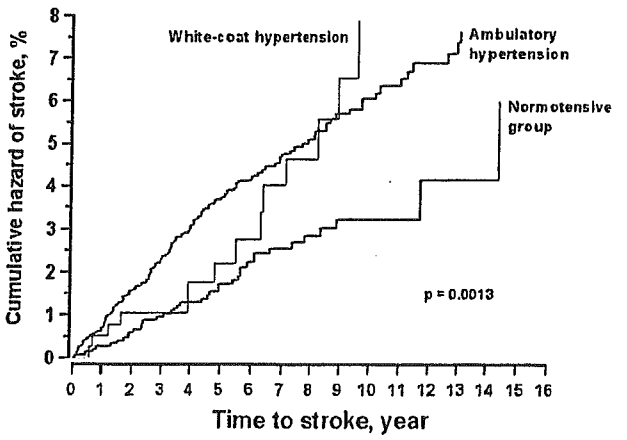

Figure 2. Cumulative hazard for stroke in the 3 groups (normotensive subjects, WCH, and ambulatory hypertension).

The crude rate of stroke (×100 person years) during the entire follow-up period was 0.35 in the normotensive group, 0.59 in the WCH group, and 0.65 in the group with ambulatory hypertension. The corresponding values up to the sixth year of follow-up were 1.06 in the normotensive group, 0.91 in the WCH group, and 1.5 in the ambulatory hypertension group. The unadjusted hazard ratios for stroke, with 95% confidence intervals (CIs), are displayed in Figure 3. Results were comparable using the 130/80 and the 135/85 mm Hg threshold values for definition of WCH.

Multivariate Analysis

In a Cox analysis (Table 4) stratified by center, WCH was associated with a nonsignificant 1.15 hazard ratio for stroke compared with the normotensive group ($P=0.658$). The no-interaction assumption of the stratified model was evaluated according to Kleinbaum[17] and found acceptable at the <0.01 level. The no-interaction assumption implies that the variables being stratified (ie, center) do not interact with the covariates in the model. When office SBP and awake SBP were forced in the same model, office BP did not yield statistical significance ($P=0.322$), and the risk of stroke increased by 2% for any 1 mm Hg increase in the awake SBP (95% CI, 1% to 3%; $P=0.0001$). The 6-year risk factor–adjusted probability of stroke in clinically normotensive individuals and in hypertensive subjects with WCH and ambulatory hypertension is depicted in Figure 4. Estimates have been made in smokers and nonsmokers for either sex.

Discussion

This study is the first to investigate the short- and long-term risk of stroke in subjects with WCH, ambulatory hypertension, and clinical normotension in a large multinational and multiethnic population. WCH was defined by an average daytime ambulatory BP <130 mm Hg SBP and <80 mm Hg DBP because in a previous analysis,[5] the risk of cardiovascular events increased in association with higher ambulatory BP levels. Average daytime levels of BP <130/80 mm Hg have been defined as definitely normotensive.[14]

During the entire follow-up period, the incidence of stroke did not differ between the WCH and the normotensive control groups. However, stroke rate showed a trend to increase after the sixth year of follow-up in the group with WCH, and the corresponding hazard curve crossed that of the ambulatory hypertension group by the ninth year of observation. Results were consistent among the different cohorts and were independent of age, sex, cigarette smoking, and previous antihypertensive medications.

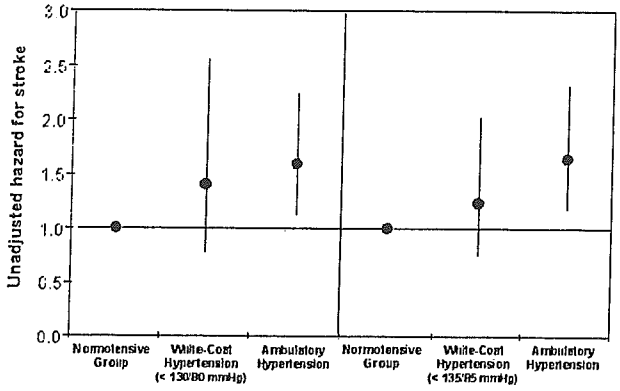

Figure 3. Unadjusted hazard for stroke in the WCH and ambulatory hypertension groups compared with the normotensive group. WCH has been defined by an average awake ambulatory BP <130/80 mm Hg (left panel) or <135/85 mm Hg (right panel).

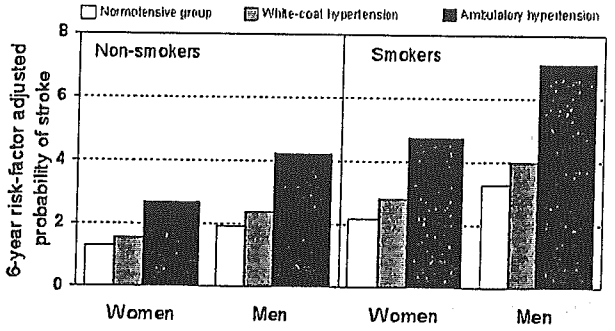

Figure 4. Six-year risk factor adjusted probability of stroke in clinically normotensive subjects and in hypertensive subjects with WCH and ambulatory hypertension. Estimates have been made in smokers and nonsmokers for either sex.

Clinical Relevance and Prognostic Value of WCH

ABPM has been approved by the US Centers for Medicare and Medicaid Services[18] for reimbursement in patients with suspected WCH. Although some outcome-based studies suggested that WCH is associated with a risk of events apparently comparable to that of clinically normotensive subjects and inferior to that of subjects with elevated daytime BP,[5–9] other studies focused on target organ damage suggested that patients with WCH may be at intermediate risk between the clinically normotensive individuals and those with ambulatory hypertension.[7,8,19–21] Therefore, the important issue of whether WCH should be considered an innocent condition remains open and unresolved.[4,22] Unfortunately, only a few data are available on the long-term natural history of WCH. In a longitudinal study, such condition evolved into ambulatory hypertension in 37% of subjects, with an accompanying rise in left ventricular mass.[23] In a study, a comparable proportion of subjects with clinical normotension and WCH evolved toward ambulatory hypertension (15% and 22%, respectively).[24]

In this study, based on 38 100 person years of observation, the highest stroke rate was noted in the clinical-based JMS-ABPM cohort, which included elderly Japanese subjects with hypertension, followed by the Ohasama cohort, which included a general Japanese population, and the PIUMA cohort, which included Italian subjects with essential hypertension. The lowest stroke rate was observed in the NYPEAP cohort, recruited in the New York area. In the absence of a significant center-covariate interaction, our findings can be reliably assumed as consistent across the different cohorts.

An unexpected finding in our study was a distinct trend toward an increased incidence of stroke in the WCH group after the sixth year of follow-up. Although substantiated only by a small number of events, these findings raise some concerns about the long-term safety of WCH. Clearly, further long-term studies are needed to clarify this aspect. In this context, it has been noted that the degree of BP rise during mental stress is a predictor of the long-term growth of atherosclerotic plaque independently of age and initial plaque area[25] Thus, it could be speculated that frequent BP peaks triggered by alerting reactions to stress may contribute to the rise in long-term risk of carotid atherosclerosis and ultimately of stroke in subjects with WCH.

Study Limitations

Because office and ambulatory BP measurements have been obtained only at entry, no information is available on the prognostic impact of serial changes in these parameters over time. In the Office versus Ambulatory Blood Pressure (OvA) study, in-treatment ambulatory BP predicted cardiovascular events independently of traditional risk factors in treated hypertensive patients.[26] However, the OvA study could not compare the predictive value of pretreatment versus in-treatment BP. In the PIUMA study, in-treatment ambulatory BP was more potent

TABLE 4. Independent Predictors of Stroke

Covariate	Comparison	Hazard Ratio	*P*-Value	95% CI
Age	1 year	1.08	0.000	1.07–1.10
Sex	Men vs women	1.57	0.003	1.17–2.12
Smoking status	Yes vs no	1.71	0.001	1.24–2.37
Previous antihypertensive treatment	Yes vs no	1.63	0.001	1.23–2.18
Ambulatory BP category				
	Normotensive group	1		
	WCH	1.15	0.658	0.61–2.16
	Ambulatory hypertension	2.01	0.001	1.31–3.08

Analysis stratified by center. WCH was defined by an average awake BP<130 mm Hg SBP and 80 mm Hg DBP.

than pretreatment ambulatory BP for cardiovascular risk stratification.[27] In the present study, a comparable number of subjects who were clinically normotensive or white-coat hypertensives at entry were receiving antihypertensive drugs during follow-up. These data suggest a comparable evolution toward the need of antihypertensive treatment in subjects with WCH and clinically normotensive controls. Finally, because data on mortality shortly after stroke were not available from all cohorts, no separate analysis could be performed on fatal and nonfatal stroke. Similarly, analyses on the different types of stroke (ie, lacunar, embolic, hemorrhagic, etc) were not possible because of insufficient standardization across the different cohorts. A substantial proportion of strokes in hypertensive subjects are attributable to lacunar infarction at the base of the brain, where short straight arteries transmit a substantial BP load from the large arteries to small resistance arteries over a very short distance.[28]

Perspectives

The long-term prognostic impact of WCH remains uncertain. In this multinational outcome-based study, we failed to detect differences in the risk of stroke between subjects with WCH and clinically normotensive controls. The risk of stroke remained consistently higher among subjects with ambulatory hypertension. However, the incidence of stroke showed a trend to increase in the long run in the group with WCH, with the corresponding hazard curve crossing that of the ambulatory hypertension group by the ninth year of follow-up. These data raise the hypothesis, to be tested in future studies, that WCH might not be a benign condition for stroke in the long term.

Acknowledgments

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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-

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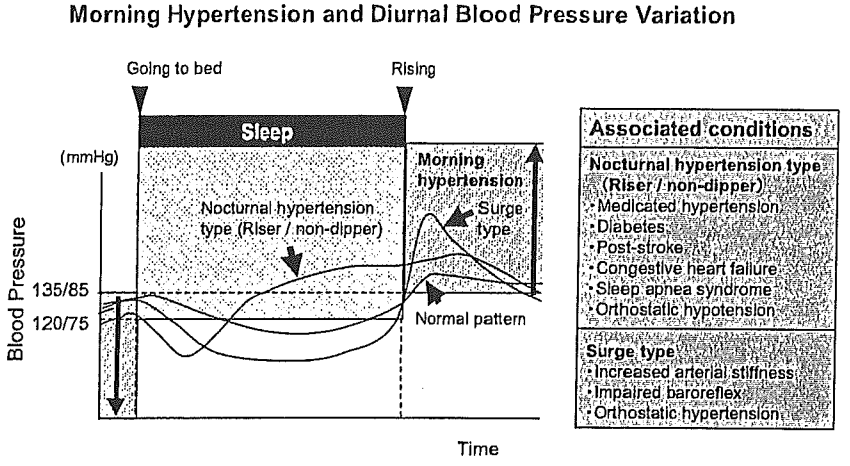

FIG. 1 Morning hypertension and diurnal blood pressure variation.

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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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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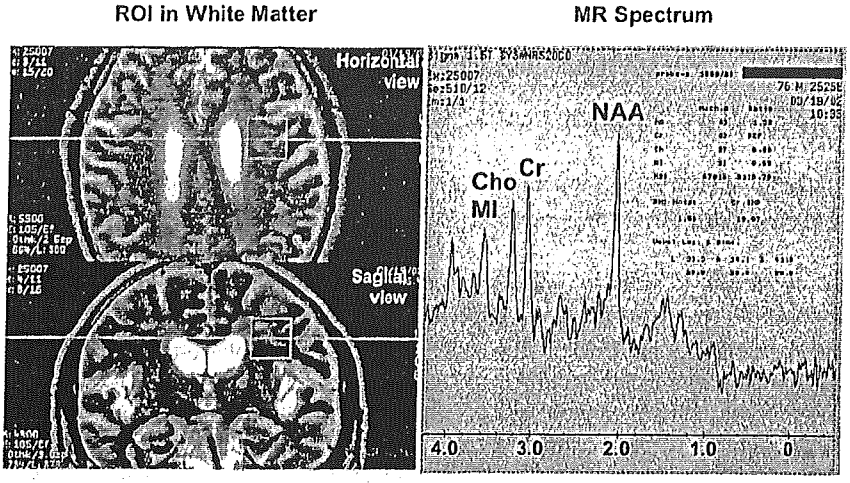

Figure 1. Region of interest (ROI) of MRS in deep white matter (left) and MRS spectrum (right) of DHT patient with advanced white matter lesion. NAA, 6.23 mmol/kg; creatine (Cr), 4.87 mmol/kg; choline (Cho), 1.33 mmol/kg. MI indicates myoinositol.

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

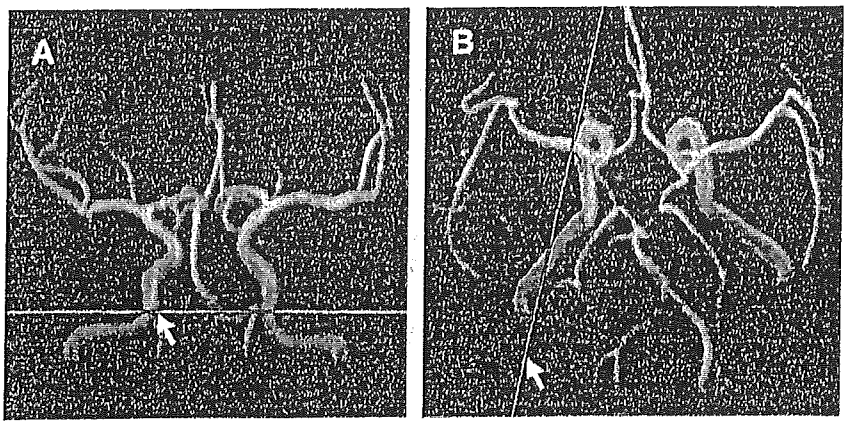

Figure 2. Portions of the ICAs (A) and MCAs (B) for quantitative MRA volume flow assessed by nontriggered PC-MRA.

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/m^2	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.