of morning BPs and preawake BPs was significant (Fig. 3). Sleep BPs were significantly reduced, but the nighttime lowest BPs were not further decreased in the bedtime-administration group. However, the differences in the reductions of ABP parameters, including preawake SBP ($p=0.186$), between the two groups were not statistically significant.

Although the morning BP surge was not significantly reduced in either group, the morning BP surge was reduced to less than 45 mmHg in all five hypertensives with exaggerated morning BP surge ≥ 45 mmHg (the highest tertile) in the bedtime-administration group. On the other hand, morning BP surge remained ≥ 45 mmHg in three of the five hypertensives with exaggerated morning BP surge in the morning-administration group.

Discussion

The present results indicate that bedtime administration of the long-acting lipophilic ACE inhibitor trandolapril is a safe and effective means of controlling morning BP in hypertensive patients without an excessive fall in nocturnal BP.

Recently, we showed that the morning BP surge was significantly associated with clinical stroke risk in hypertensive patients (*32*). This association was independent of age, 24-h BP level, and silent cerebral infarct (*32*), which is a powerful predictor of clinical stroke events (*34*, *35*). In addition to the morning BP surge, the morning BP level is also an important predictor of stroke events in hypertensive patients (*32*). In this study, bedtime administration of trandolapril significantly reduced morning BP levels after waking. In addition, the prewaking BP was also significantly reduced by the bedtime administration. On the other hand, the morning administration of trandolapril significantly reduced awake BP, but the reduction of morning and preawake BPs was limited. Thus, the bedtime administration of trandolapril could be a specific treatment for reducing morning BP.

There have been several studies of antihypertensive medications specific for morning BP. Long-acting effects are the most important characteristic for sufficient morning BP control by once-daily use of antihypertensive medication (*29*, *36*, *37*). Antihypertensive therapy should provide the most effective protection at the time of the greatest risk, that is, in the morning hours. Pharmacokinetically, an extended-release form of verapamil was also reported to be highly effective for BP reduction (*38*). In addition, it may be possible to achieve more specific chronological treatment for morning BP surge by using an antihypertensive medication which reduces the pressor effect of neurohumoral factors potentiated in the morning, such as inhibitors of the sympathetic activity or the renin-angiotensin system. α-Adrenergic blockers and $\alpha\beta$-blockers might be effective for reducing morning BP surge in hypertensive patients. Bedtime administration of α-adrenergic blockers has the most marked BP-lowering effect in the morning (*39*). This study also demonstrated the potential benefit of bedtime ACE inhibitors for controlling morning BP in clinical practice for hypertensive patients.

Nighttime administration of the ACE inhibitor trandolapril appears to be more effective than morning administration for specifically controlling morning SBP. However, we cannot state this conclusively based on the present results. The differences in the reductions of ABP parameters, including preawake SBP, between the two groups did not reach the level of statistical significance. One of the limitations of this study was the lack of a control group. Thus, the reproducibility of each ABPM parameter was not sufficiently clear to render the results conclusive. Other, shorter-acting ACE inhibitors might increase the difference between the two groups due to the weaker BP-lowering effect of the morning administration. Because of its lipophilic nature, trandolapril has the longest-acting ACE inhibitory activity and BP-lowering effect of all the ACE inhibitors (*40*). In fact, the 24-h BP-lowering effects were comparable among the two groups. However, awake BP was not significantly reduced in the bedtime-administration group. A longer-acting BP-lowering effect is the most important effect for an antihypertensive medication, and in addition, for those with higher morning BP level, bedtime administration seems an alternative or additional antihypertensive strategy.

Recently, it has been demonstrated that, in addition to circulating factors, the tissue renin-angiotensin-aldosterone secretion of the cardiovascular system exhibits diurnal variation (*41*), possibly in relation to a clock gene (*42*, *43*). In addition to the reduction of the morning BP level, the morning activation of the tissue renin-angiotensin-aldosterone system might be effectively suppressed by bedtime administration of an ACE inhibitor, leading to more effective protection against hypertensive target organ damage and cardiovascular events in hypertensive patients.

The bedtime administration of antihypertensive medication has the potential hazard of ischemia of target organs because of excessive nocturnal BP reduction. Extreme-dippers with marked nocturnal BP falls have increased potential risk for ischemic cardiovascular events when treated with strict antihypertensive medication or specific medication just before going to bed (*10*, *44*). Since it has been reported that ACE inhibitor reduced normal BP levels further in white-coat hypertensive patients (*45*), we expected the nighttime lowest BP levels to be reduced further by bedtime administration of trandolapril. However, the nighttime lowest BP was not further decreased, although the average sleep BP decreased, particularly in the preawake period. Thus, bedtime administration of trandolapril can be considered safe with respect to ischemia of target organs during sleep.

In conclusion, bedtime administration of the long-acting ACE inhibitor trandolapril was effective for controlling morning BP and was suggested to be safe in the sense that it caused no marked nocturnal BP reduction in hypertensive patients.

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Type 2 Diabetes Is Associated With Left Ventricular Concentric Remodeling in Hypertensive Patients

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Background: Left ventricular (LV) geometric remodeling is associated with cardiovascular prognosis in hypertensive patients. It is uncertain how LV remodeling is modulated by diabetes in hypertensive patients. In this study, we investigated the impact of diabetes and ambulatory blood pressure (BP) on LV geometric remodeling in hyptensives with/without diabetes.

Methods: Ambulatory BP monitoring and echocardiography were performed to compare 24-h BP levels and LV measurements in 400 uncomplicated hypertensives (mean age, 67 years, 152 men and 248 women) between diabetic (n = 161) and nondiabetic (n = 239) patients.

Results: The age (67 *v* 68 years), percentage of men (43% *v* 34%), body mass index (24.5 *v* 24.0 kg/m^2), 24-h systolic BP (144/80 *v* 144/82 mm Hg), LV mass index (128 *v* 130 g/m^2) were similar between the groups. Diabetic patients had higher relative wall thickness (0.50 *v* 0.44, $P < .001$) and higher prevalence of concentric LV hypertrophy (39.4% *v* 26.8%, $P < .001$) than nondiabetic patients. The presence of diabetes (odds ratio [OR] = 2.76; 95% confidence interval [CI] = 1.73–4.41, $P < .001$) and 24-h systolic BP (OR for 10 mm Hg increase = 1.17; 95% CI = 1.01–1.37, $P < .05$) were independently associated with the higher relative wall thickness (≥0.45). On the other hand, 24-h systolic BP was independently associated with LV hypertrophy (OR for 10 mm Hg increase = 1.32; 95% CI = 1.14–1.52, $P < .05$).

Conclusions: Among hypertensive patients, type 2 diabetes was associated with concentric LV geometry independent of ambulatory BP. Am J Hypertens 2005;18: 23–29 © 2005 American Journal of Hypertension, Ltd.

Key Words: Type 2 diabetes, hypertension, concentric hypertrophy, left ventricular geometric remodeling, ambulatory blood pressure monitoring.

Diabetes mellitus is one of the most important risk factors for cardiovascular disease.[1] Diabetes mellitus and hypertension frequently coexist and each pathologic condition exacerbates the other.[2] Several population studies have shown that diabetes is associated with left ventricular (LV) structural and functional abnormalities.[3–5] In the Hypertension genetic epidemiology network (HyperGEN) study[4] and the Strong Heart Study,[5] type 2 diabetes was associated with higher LV mass, more concentric LV geometry, and lower cardiac function. Because there is a strong relationship between LV hypertrophy and adverse cardiovascular outcomes in hypertensive patients,[6–8] early detection of LV structural changes in diabetic patients may be important.

The level of blood pressure (BP) using ambulatory BP monitoring correlates better than clinic BP measurements with hypertensive target organ damage.[9] Patients with white coat hypertension, defined as persistent clinic hypertension but normal 24-h BP with ambulatory BP monitoring, have smaller LV mass than patients with sustained hypertension. The LV mass of the former is similar to that of normotensive patients.[10] Although diabetes and hypertension both may be contributing factors to LV remodeling, there are few reports showing the impact of ambulatory BP on LV remodeling in diabetic patients.

Thus we performed a cross-sectional study to assess the association of diabetes and ambulatory BP with LV geometric remodeling in Japanese hypertensive patients with and without diabetes.

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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).

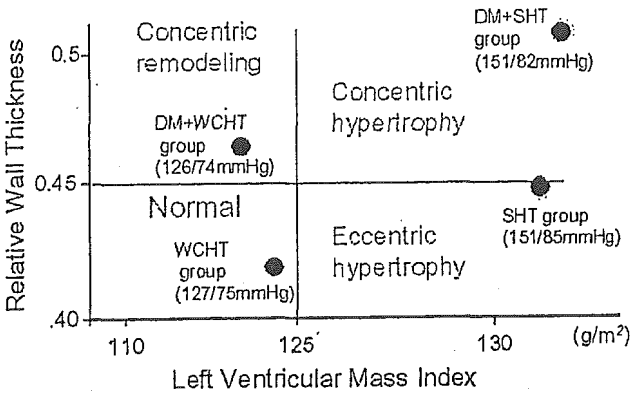

FIG. 1 Characteristics of the LV geometric remodeling pattern in each group. The average values of left ventricular mass index and relative wall thickness were plotted for each group. SHT = sustained hypertension (24-h systolic BP ≥135 mm Hg); WCHT = white coat hypertension (24-h systolic BP <135 mm 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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Potential of free-form TFPI and PAI-1 to be useful markers of early atherosclerosis in a Japanese general population (the Suita Study): association with the intimal-medial thickness of carotid arteries

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Abstract

This study assessed markers of vascular endothelial cell dysfunction associated with early atherosclerosis in carotid arteries. We measured the plasma levels of free-form tissue factor pathway inhibitor (free TFPI), plasminogen activator inhibitor-1 (PAI-1), and von Willebrand factor (vWF) in 522 adults without cardiovascular disease enrolled in the Suita Study. For each sex, we analyzed the association of the degree of intimal-medial thickness (IMT) with hemostatic markers using logistic regression analysis considering potential confounding risk factors, including age, body mass index, lifestyle (current smoking and drinking), illness (diabetes mellitus and hyperlipidemia), systolic blood pressure, and antihypertensive drug use. The age-adjusted levels of free TFPI and PAI-1 were positively and independently associated with the degree of IMT for men. Even after adjustment for all confounding factors, the level of PAI-1 was positively associated with the degree of IMT. These results indicate that measurement of the levels of free TFPI and PAI-1 is a potentially useful tool for the detection of early atherosclerosis in men.

Keywords: Atherosclerosis; Endothelium-derived factors; Hypertension

1. Introduction

Measurement of the intimal-medial thickness (IMT) of carotid arteries has been used as a non-invasive endpoint in epidemiological studies and clinical trials to assess the progression and regression of atherosclerosis [1,2]. Furthermore, IMT has recently been used not only as a surrogate endpoint for atherosclerosis of the coronary artery but also as a good indicator of the presence and extent of coronary artery disease [3–6]. Case-reference studies in a general population have been performed in regard to the association between markers of vascular endothelial cell dysfunction and atherosclerosis by measuring IMT of the carotid artery [7–9]. However, to detect early atherosclerosis, it is essential to study the association between these markers and the extent of atherosclerosis, using a general population free from cardiovascular disease (CVD).

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In this study, we focused on the association between three markers of endothelial cell dysfunction, namely free-form tissue factor pathway inhibitor (free TFPI), plasminogen activator inhibitor-1 (PAI-1), and von Willebrand factor (vWF) and IMT of carotid arteries in a Japanese general population (the Suita Study). Plasma concentrations of vWF and PAI-1 have previously been used as surrogate markers of endothelial damage [10,11]. TFPI inhibits tissue factor-initiated coagulation by binding to factor Xa and tissue factor-activated factor VII complex [12,13]. Most TFPI is synthesized by vascular endothelial cells, and is distributed into at least four pools in vivo. The majority of TFPI synthesized by vascular endothelial cells is associated with endothelial cells, whereas other pools circulate in the blood as complexes with lipoproteins (Lp-TFPI) or as a free form (free TFPI). A minor pool of TFPI is present in platelets. It has been demonstrated that free TFPI strongly correlates with endothelial cell markers such as thrombomodulin, vWF, and tissue-type plasminogen activator, whereas total TFPI does not [14]. There is a strong, positive correlation between the free TFPI and endothelial cell-associated TFPI levels [15]. Therefore, we selected free TFPI as a marker of endothelial cell dysfunction, instead of Lp-TFPI or total TFPI.

Here, we have demonstrated the potential of free TFPI and PAI-1 to be useful markers of early atherosclerosis by studying their association with IMT in relation to conventional risk factors for CVD.

2. Methods

2.1. Study population

The study population was based on samples randomly selected from the residents of Suita, a city located in the second largest urban area in Japan (the Suita Study) [5]. The subjects have been visiting the National Cardiovascular Center every 2 years since 1989 for regular health checkups. Only subjects who provided written informed consent to have a blood examination were enrolled in this study. The subjects included 245 men and 277 women who were free of cardiovascular disease, aged from 34 to 91 years, and attended the National Cardiovascular Center from 5 August 1998 to 24 December 1998. Subjects were classified as smokers if they smoked at least one cigarette per day. Subjects were defined as hypertensive if their diastolic blood pressure was $\geq$95 mmHg, their systolic blood pressure was $\geq$160 mmHg, or they were taking antihypertensive medication. Subjects whose fasting blood glucose levels were $\geq$7.78 mmol/L, whose blood glucose levels were $\geq$11.11 mmol/L 2 h after a 75-g oral glucose loading, or who were taking antidiabetic medication were defined as diabetic. Subjects whose total serum cholesterol level was $\geq$5.68 nmol/L (220 mg/dl), or who were taking anti-hypercholesterolemic medication were defined as having hypercholesterolemia.

2.2. IMT measurements

The details of the ultrasonic carotid examination have previously been published [16]. We used a high-resolution B-mode ultrasonic machine with 7.5-MHz transducers, yielding an axial resolution of 0.2 mm. The regions between 30 mm proximal from the beginning of the dilation of the bifurcation bulb and 15 mm distal from the flow divider of both common carotid arteries were scanned. All measurements were made at the time of scanning using the instrument's electronic caliper and were recorded as photocopies. The IMT in common carotid arteries was measured on a longitudinal scan of the common carotid arteries at a point 10 mm proximal from the beginning of the dilation of the bifurcation bulb. We defined the IMT as mean IMT of the near and far walls at the point of measurement.

2.3. Blood collection and analysis

After a minimum 12-h fast and between 10 a.m. and 1 p.m., blood samples for hemostatic profile were collected into disposable, siliconized, evacuated glass tubes containing 0.1 vol. of 3.13% trisodium citrate, and blood collected in a second tube was used for the coagulation assay. The samples were centrifuged at 4600 $\times$ g for 10 min at room temperature within 1 h of collection. The PAI-1 antigen level was immediately determined, and the remaining plasma was aliquoted in plastic tubes and stored at -80 °C until use. The thawed samples were used to measure free TFPI and vWF.

The antigen level of free TFPI was measured by a sandwich enzyme immunoassay method [17]. The coefficient of intra-assay variation for the assay was 2.7%. The antigen levels of PAI-1 and vWF were automatically measured by latex photometric immunoassay using an LPIA-tPAI kit (Mitsubishi Kagaku Medical) and STA liatest vWF kit (Diagnostica Stago), respectively. The coefficients of intra-assay variation of PAI-1 and vWF were 1.0 and 4.3%, respectively.

2.4. Statistical analysis

All statistical analyses were performed independently by sex. We first used Spearman correlation analysis to assess the association between the progression of IMT and the analyzed parameters (Tables 1 and 2). We then used ANCOVA to investigate whether plasma levels of free TFPI, PAI-1, and vWF are positively and independently associated with the degree of carotid intimal thickness or not (Table 3). We have performed two types of adjustments. First, adjustments were made for age only. Second, further adjustments were made for lifestyle (drinking and smoking), illness (diabetes, hypercholesterolemia), body mass index, systolic blood pressure, and antihypertensive drug use. Differences with a value of $P < 0.05$ for ANCOVA were

Table 1
Demographic characteristics and unadjusted hemostatic parameters according to rank of intimal-medial thickness (IMT) of the carotid artery in men

	IMT-rank				P
	Q1 ($n = 58$)	Q2 ($n = 70$)	Q3 ($n = 57$)	Q4 ($n = 60$)	
Median of IMT (mm)	0.73	0.83	0.93	1.05	
Age (year)	47.4 ± 7.8	59.2 ± 9.2	69.2 ± 8.7	70.4 ± 8.0	<0.0001
Current drinking (%)	79	73	67	62	<0.0009
Smoker (%)	78	73	67	62	<0.0007
Body mass index (kg/m^2)	23.2 ± 3.3	23.7 ± 3.2	23.4 ± 3.3	22.8 ± 3.1	<0.4217
Diabetes (%)	0	3	5	10	<0.0511
Hypertension (%)	7	29	32	45	<0.0001
Hypercholesterolemia (%)	7	11	9	15	<0.1685
LDL-cholesterol (mg/dl)	113.9 ± 27.5	124.8 ± 29.5	120.3 ± 26.7	131.0 ± 26.4	<0.0060
HDL-cholesterol (mg/dl)	60.8 ± 17.2	56.1 ± 12.5	55.2 ± 16.1	55.2 ± 16.1	<0.0255
Free TFPI (ng/ml)	15.7 ± 4.5	16.0 ± 3.8	17.2 ± 3.2	18.2 ± 4.6	<0.0006
PAI-1 (ng/ml)	32.3 ± 25.2	32.9 ± 30.9	29.3 ± 19.7	33.0 ± 38.8	<0.2059
von Willebrand factor (%)	115.0 ± 43.7	137.1 ± 45.9	151.7 ± 54.9	160.8 ± 63.9	<0.0001

Values are mean ± S.D. or percent. *P*-values were calculated by simple linear regression analysis. TFPI; tissue factor pathway inhibitor, PAI-1; plasminogen activator inhibitor-1.

Table 2
Demographic characteristics and unadjusted hemostatic parameters according to rank of intimal-medial thickness (IMT) of the carotid artery in women

	IMT-rank				P
	Q1 ($n = 66$)	Q2 ($n = 73$)	Q3 ($n = 63$)	Q4 ($n = 75$)	
Median of IMT (mm)	0.70	0.78	0.85	0.95	
Age (year)	45.8 ± 6.7	55.2 ± 7.6	62.2 ± 7.2	71.9 ± 7.8	<0.0001
Current drinking (%)	45	33	35	25	<0.0897
Smoker (%)	12	5	5	8	<0.6107
Body mass index (kg/m^2)	21.3 ± 2.5	21.6 ± 2.9	23.2 ± 3.5	22.9 ± 3.6	<0.0145
Diabetes (%)	2	0	5	4	<0.6649
Hypertension (%)	2	10	19	40	<0.0001
Hypercholesterolemia (%)	8	10	11	19	<0.0913
LDL-cholesterol (mg/dl)	115.4 ± 30.5	126.4 ± 30.0	137.9 ± 25.7	137.0 ± 26.5	<0.0001
HDL-cholesterol (mg/dl)	73.1 ± 17.9	69.2 ± 15.5	67.5 ± 16.7	62.1 ± 14.8	<0.0002
Free TFPI (ng/ml)	11.5 ± 3.2	14.9 ± 5.0	16.3 ± 4.2	17.5 ± 4.8	<0.0001
PAI-1 (ng/ml)	20.2 ± 18.3	19.8 ± 12.8	25.7 ± 19.1	26.2 ± 18.0	<0.0707
von Willebrand factor (%)	107.8 ± 31.4	126.5 ± 41.8	136.5 ± 51.6	157.2 ± 59.2	<0.0001

Values are mean ± S.D. or percent. *P*-values were calculated by simple linear regression analysis. TFPI; tissue factor pathway inhibitor, PAI-1; plasminogen activator inhibitor-1.

considered to be significant. All analyses were performed with SAS statistical software (release 8.2 SAS Institute Inc).

3. Results

3.1. Demographic characteristics and unadjusted parameters according to rank of IMT of carotid arteries

We measured IMT in a general population, divided it into four quartiles by sex, and analyzed the demographic characteristics and unadjusted parameters according to IMT rank, as shown in Tables 1 and 2. The IMT median of each quartile (*Q*1, *Q*2, *Q*3 and *Q*4) is shown in the first column of each table. In both sexes, the plasma levels of free TFPI, vWF, and LDL-cholesterol as well as age and hypertension increased in a stepwise manner from the first to the forth IMT quartile.

3.2. Multivariate analysis of free TFPI, PAI-1, and vWF levels according to IMT rank

As summarized in Table 3, we analyzed the plasma levels of free TFPI, PAI-1, and vWF according to IMT ranks after either adjusting for age only or adjusting for age, lifestyle (drinking and smoking), body mass index, systolic blood pressure, diabetes, hypercholesterolemia, and hypertensive drug use. Age adjusted free TFPI levels in men increased in a stepwise manner from the first to the fourth IMT quartile ($P = 0.003$, for trend) and the levels of free TFPI in the third and the fourth quartiles compared to the lowest IMT quartile remained statistically significant in the multivariate analysis. However, the statistically significant increases of free TFPI

Table 3
Adjusted mean levels of free TFPI, PAI-1, and von Willebrand factor according to rank of intimal-medial thickness (IMT) of the carotid artery

	IMT-rank				*P* for trend
	*Q*1	*Q*2	*Q*3	*Q*4	
Free TFPI (ng/ml)					
Men					
Age adjusted	15.3 ± 0.7	15.9 ± 0.5	17.5 ± 0.5‡	18.4 ± 0.6‡	0.003
All adjusted	16.2 ± 0.7	15.9 ± 0.5	17.2 ± 0.6	17.9 ± 0.6	0.075
Women					
Age adjusted	14.3 ± 0.7	15.8 ± 0.5‡	15.6 ± 0.5	14.8 ± 0.6	0.410
All adjusted	14.9 ± 0.6	15.9 ± 0.5	15.2 ± 0.5	14.5 ± 0.6	0.250
PAI-1 (ng/ml)					
Men					
Age adjusted	21.9 ± 4.9	31.1 ± 3.5	35.1 ± 4.2	39.8 ± 4.3‡	<0.001
All adjusted	24.1 ± 5.3	30.8 ± 3.5	34.7 ± 4.3	38.3 ± 4.5	<0.001
Women					
Age adjusted	18.0 ± 2.9	19.1 ± 2.1	26.3 ± 2.2‡	28.4 ± 2.7‡	0.227
All adjusted	20.3 ± 2.6	20.8 ± 1.9	23.7 ± 2.0	26.9 ± 2.5	0.317
von Willebrand factor (%)					
Men					
Age adjusted	144.0 ± 8.3	142.1 ± 6.0	135.6 ± 7.2	143.0 ± 7.3	0.353
All adjusted	141.3 ± 8.9	142.1 ± 6.0	136.9 ± 7.3	144.4 ± 7.7	0.180
Women					
Age adjusted	133.7 ± 7.6	134.0 ± 5.5	130.8 ± 5.9	131.8 ± 7.1	0.042
All adjusted	133.5 ± 7.7	134.7 ± 5.7	129.9 ± 6.0	132.0 ± 7.4	0.049

Values are mean ± errors adjusted for age or adjusted for age, life style (current drinking and smoking), body mass index, present illness (diabetes, hypercholesterolemia), systolic blood pressure, and hypertensive drug use. (‡) $P < 0.05$ compared with Q1 subjects. TFPI; tissue factor pathway inhibitor, PAI-1; plasminogen activator inhibitor-1.

levels in men were not detected after adjustment for several possible confounding factors (all adjusted). The free TFPI levels in women demonstrated a mountain-shaped relationship with the degree of IMT in the multivariate analysis.

Age-adjusted PAI-1 levels in men increased with increasing IMT rank ($P < 0.001$) and the levels in the fourth quartile compared to the lowest IMT quartile remained statistically significant in the multivariate analysis. Age-adjusted PAI-1 levels in women also increased with increasing IMT rank and the levels in the third and fourth quartiles compared to the lowest quartile were statistically significant, although the *P* value for trend was 0.227. The statistically significant increases of PAI-1 levels in men was detected after all adjustments.

In contrast, the age-adjusted vWF levels in both sexes did not show significant changes among IMT quartiles, although the *P* values for trend in women after all adjustments were significant. These results indicate that measurement of the levels of free TFPI and PAI-1 is a potentially useful tool for the detection of early atherosclerosis in men.

4. Discussion

In this cross-sectional analysis, we have demonstrated that increased levels of free TFPI and PAI-1 in men without CVD were closely associated with the elevation of IMT in common carotid arteries as measured by B-mode ultrasonography. These findings suggest that free TFPI and PAI-1 may be sensitive markers reflecting early atherosclerosis in the carotid arteries.

It has been demonstrated that TFPI localizes with tissue factor within atherosclerotic plaques in human carotid and coronary arteries and modulates the thrombogenicity of the plaque by attenuating the tissue factor activity [18–20]. Enhancement of TFPI expression in the atherosclerotic plaque will cause an increase in the free TFPI concentration in the plasma of patients with cardiovascular disease. In fact, elevated free TFPI levels have been reported in the plasma of patients with ischemic heart disease [21,22]. These findings imply that an elevated level of free TFPI in the plasma is closely associated with hypercoagulable states in atherosclerotic diseases. However, the role of TFPI associated with subclinical or early atherosclerosis was rarely reported. Sakkinen et al. reported a significant positive relationship between the level of plasma TFPI activity and subclinical cardiovascular disease in a healthy elderly cohort study [23]. However, the relationship between age/gender and TFPI levels in a general population has not been examined in detail. In this study, we have extended the above results and demonstrated a direct link between the extent of carotid artery atherosclerosis and the plasma level of free TFPI antigen in men in a Japanese general population without CVD.

As summarized in review articles [24,25], many investigators have demonstrated the crucial role of PAI-1 in human atherothrombosis. High plasma PAI-1 concentrations are associated with various thrombotic diseases and are independent risk factors for myocardial infarction, as has been proven by epidemiological studies. Animal experiments using PAI-1 transgenic mice and PAI-1 knock-out mice also support the role of PAI-1 in the progression of atherosclerosis [26–28]. These previous findings suggest that an increased PAI-1 level in the plasma is closely associated with the progression of atherosclerotic conditions. Here, we have demonstrated that this relationship could also be observed in early atherosclerotic conditions in a general population.

We have previously reported that the mean IMT value of both sexes increased stepwise with the number of major coronary risk factors, namely hypertension, smoking, and hypercholesterolemia [5]. It has also been reported that PAI-1 levels were increased in patients with early hypertension, and that these elevated PAI-1 levels were improved by treatment with angiotensin-converting enzyme inhibitor [29]. Recently, it has been reported that PAI-1 deficiency prevents hypertension and vascular fibrosis in response to long-term nitric oxide synthase inhibition [30]. Taken together, these data indicate that early atherosclerotic conditions or endothelial cell dysfunction are induced by hypertensive conditions, resulting in elevation of the plasma levels of free TFPI and PAI-1. Therefore, it is thought that the close association between elevation of the plasma levels of free TFPI and PAI-1 and hypertensive conditions probably diminished the statistically independent association between plasma levels of free TFPI and PAI-1 and the degree of IMT.

In conclusion, we have demonstrated that the levels of free TFPI and PAI-1 in men increased with the degree of IMT. Therefore, we propose that free TFPI and PAI-1 are potentially useful markers for detecting early atherosclerosis. However, prospective studies are necessary to clarify whether these markers are predictive of the onset of atherosclerotic diseases in Japanese people.

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Case Report

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

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

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

Case Report

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

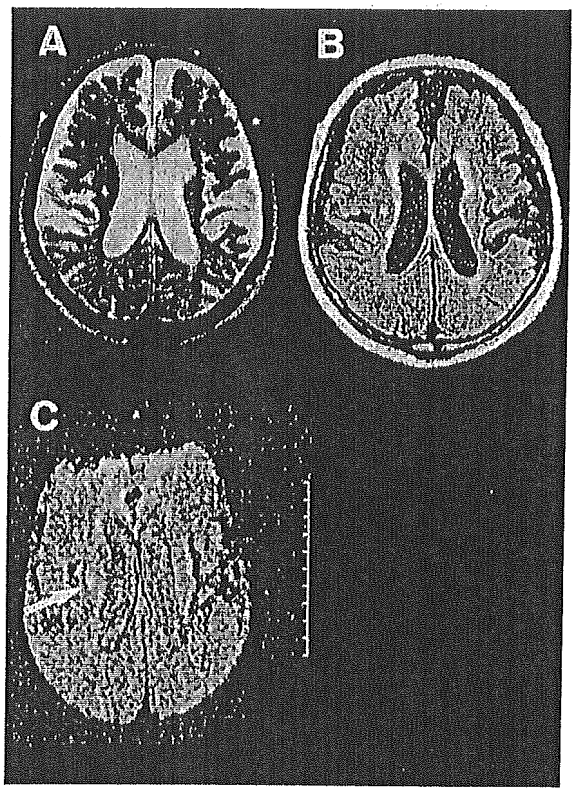

FIG. 1. Brain magnetic resonance (MR) imaging 1 month after the episode revealed multiple cerebral infarcts. (**A**) T2-weighted imaging; (**B**) flair imaging. Diffusion MR imaging revealed a new infarct corresponding to a neurologic deficit (**C, arrow**) in this patient.

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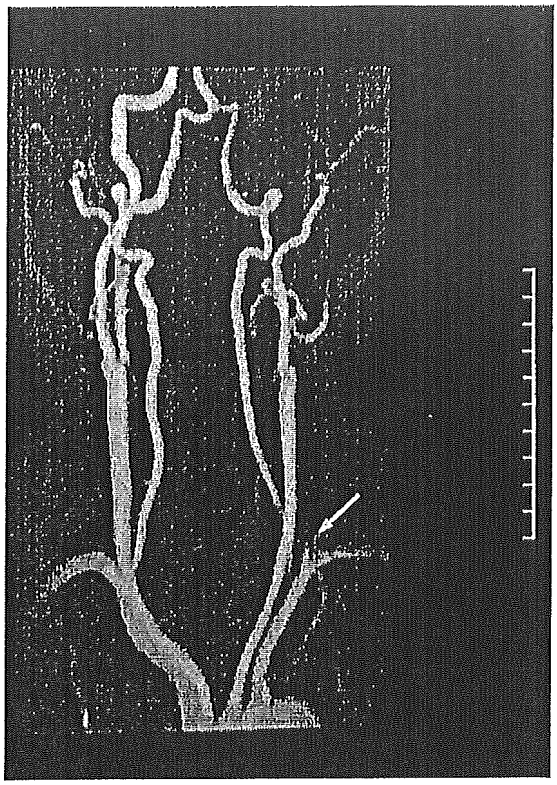

FIG. 2. Brain MR angiography disclosed total occlusion of the left internal carotid artery (**arrow**).

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

Discussion

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

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

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

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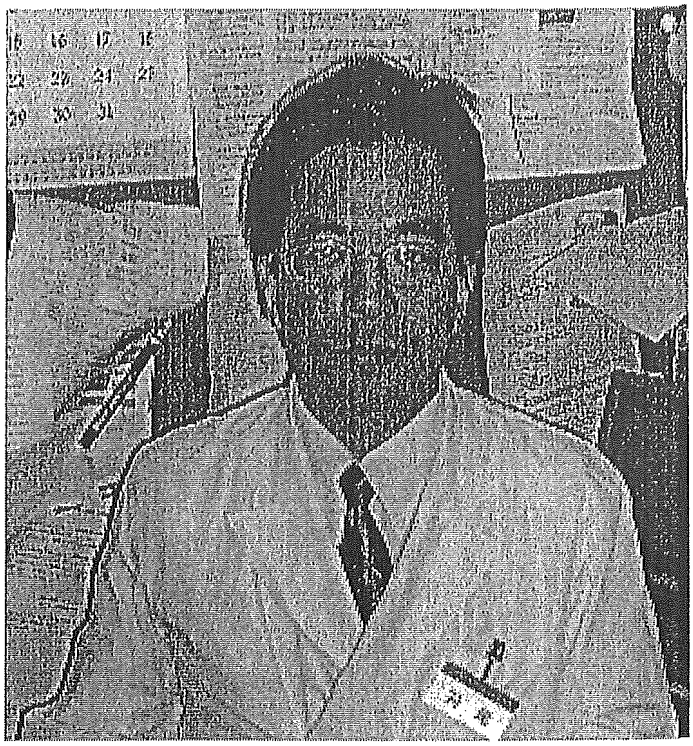

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Hypertension and its clinical implications for morning renin–angiotensin system control

Interview with
Dr Kazuomi Kario,
Jichi Medical School,
Tochigi, Japan
By Angela Bellamy

Dr Kario's contribution to cardiology is widely recognized: he is a fellow of the Japanese Society of Internal Medicine, the Japan Geriatrics Society, the American College of Cardiology, the American College of Physicians, the American Heart Association, and the Council for High Blood Pressure Research. He is currently the executive editor of *Hypertension Research*, the official journal of the Japanese Society of Hypertension, and on the editorial boards of *Circulation Journal*, the official journal of the Japanese Circulation Society, and *Hypertension*, the official journal of the American Heart Association.

Dr Kario's research interests include ambulatory monitoring of biomechanical information to assess cardiovascular-event triggers, and he is a leading authority in the new research field of psychoneurocardiology, which focuses on the impact of cerebrovascular disease on cardiovascular disease. He has published more than 200 academic papers.

Summary

Hypertension remains one of the world's most serious public-health issues despite more widespread use of antihypertensive treatments. Rates of decline of deaths from coronary heart disease (CHD) and stroke have slowed in the past decade. The prevalence of and hospitalization rates for heart failure, wherein the majority of patients have hypertension before developing heart failure, have continued to increase. In addition, there is an increasing trend in end-stage renal disease as primary diagnosis. Preventing the development of end-organ damage in patients with hypertension appears to require both effective blood pressure management and interventions that interfere with the renin–angiotensin–aldosterone system (RAAS). Angiotensin II receptor blockers (ARBs) are effective antihypertensives and may offer end-organ protection beyond their blood-pressure-lowering effects. Ongoing studies will help to better characterize these benefits in patients with multiple cardiovascular risk factors.

Introduction

Hypertension has become one of the world's most pressing medical and public-health issues. It has been estimated that more than one-half of the population aged over 60 years has hypertension, and that three-quarters of people aged 70 years or older have the condition.[1] Prevalence of hypertension appears to be higher in non-Hispanic black populations than in white populations and slightly higher in women than in men.[1] Although earlier studies have suggested that the prevalence of hypertension is declining,[2] more recent reports indicate that the opposite is true.[3]

Hypertension is the most important modifiable risk factor for coronary artery disease, stroke, congestive heart failure, and end-stage renal disease (ESRD), and, for this reason, it has been the target of extensive research, widespread patient education, and a concerted global effort on behalf of the medical community to reduce its prevalence and prevent its potentially life-threatening consequences. The recently published Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[4] highlights considerable success in terms of improved awareness of hypertension among the general public and more widespread use of antihypertensive treatments, and this, the report claims, has played a vital role in the declining death rates from stroke, coronary heart disease (CHD), and heart failure. Nevertheless, despite these encouraging signals, the report also points to the fact that the rate of decline of deaths from CHD and stroke has slowed over the past decade – despite more widespread use of antihypertensive agents – and that significantly more patients are now presenting with ESRD as the primary diagnosis.[4]

"This is an extremely worrying trend," says Dr Kazuomi Kario, "and one that has led us to believe that factors other than blood pressure have a negative impact on long-term cardiovascular and renal health.

"It seems that simply reducing blood pressure without also protecting the kidneys, heart, and cerebral vasculature from other damaging local influences may mean we are not reducing the morbidity and mortality associated with hypertension as much as we would like."

Blood pressure and cardiovascular risk

Numerous epidemiological and clinical studies from around the world attest to a strong, graded, and consistent relationship between blood pressure and renovascular disease.[5]

Recent observational studies have indicated that, throughout middle and old age, risk of vascular mortality increases progressively and linearly from blood pressures as low as 115 mmHg systolic and 75 mmHg diastolic.[6] Longitudinal data from the Framingham Heart Study also indicate that blood pressures in the range of 130–139/85–89 mmHg are associated with a more than 2-fold increase in the relative risk of cardiovascular disease compared with those below 120/80 mmHg.[7]

All these data suggest that cardiovascular complications are the result of blood pressures that were previously considered to be normal, and this has led to a recent reclassification of blood pressure by the JNC that now includes the term 'prehypertension' for those individuals with blood pressures from 120 to 139 mmHg systolic and/or 80 to 89 mmHg diastolic (Table).[4]

BP classification	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	< 120	and < 80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	≥ 160	or ≥ 100

Table. *Revised classification of blood pressure (BP) for adults.*[4]

"Prehypertension is not a disease category, but rather a term used to identify individuals at high risk of developing hypertension," explains Dr Kario. "These individuals are not candidates for drug therapy, but they are certainly candidates for lifestyle interventions that reduce their risk of developing hypertension in the future."

Another relatively recent finding is that 24-hour blood pressure variability has a direct effect on the severity and rate of progression of end-organ damage.[8] Studies have shown that hypertensive patients who do not exhibit a nocturnal reduction in blood pressure have a higher incidence of end-organ damage than patients who do.[8]

In addition, since the majority of cardiovascular events occur between 06:00 and noon,[9] there is increasing speculation that the morning blood pressure surge contributes directly to target-organ damage and cardiovascular risk in patients with hypertension.[10,11]

Interestingly, the rapidity of the blood pressure surge may also be an independent predictor of events.[12] "Our own research in over 500 elderly hypertensive individuals has shown that patients with pronounced rates of rise of blood pressure during the time of arousal from sleep are significantly more likely to experience stroke and have magnetic resonance imaging evidence for infarct in the brain," says Dr Kario. "We have shown that just a 10-mmHg increase in the morning systolic blood pressure surge increases the risk of stroke by over 20%, and this is consistent with the findings of other groups."[13]

Dr Kario believes that ambulatory blood pressure monitoring (ABPM) is a very effective way of predicting which hypertensive patients are at greatest risk of cardiovascular events.[14] "ABPM is a highly useful diagnostic tool because it can detect both non-dipping and morning surging as well as helping to distinguish masked hypertension, white-coat hypertension and sustained hypertension," he says. "It also has far greater prognostic strength than a single blood pressure measurement taken in the clinic."

"It seems that simply reducing blood pressure without also protecting the kidneys, heart, and cerebral vasculature from other damaging local influences may mean we are not reducing the morbidity and mortality associated with hypertension as much as we would like"