Is the absence of a normal nocturnal fall in blood pressure (nondipping) associated with cardiovascular target organ damage?

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Objective **To determine whether the failure to decrease blood pressure normally during sleep is associated with more prominent target organ damage.**

Methods **Cardiac and vascular structure and function were characterized in 183 asymptomatic, unmedicated hypertensive patients and compared with their ambulatory blood pressures.**

Results **The 104 patients with a normal (> 10%) nocturnal fall in systolic blood pressure (dippers) were similar to the 79 patients with an abnormal fall (nondippers) in sex, race, body size, smoking history, and average awake ambulatory blood pressure. Nondippers tended to be older (57 versus 54 years, $P = 0.06$). The supine blood pressure upon completion of the ultrasound studies was higher in the nondippers (156/93 versus 146/89 mmHg, $P < 0.005$) as was the variability of the awake diastolic blood pressure. There were no differences between dippers and nondippers in left ventricular mass (170 versus 172 g), mass index (90 versus 91 gm/m^2), prevalence of abnormal ventricular geometry, common carotid artery diameter (5.74 versus 5.75 mm), and vascular strain. Although nondippers were more likely to have carotid artery plaque (41 versus 27%, $P = 0.053$) and an increased intimal–medial thickness (0.84 versus 0.79 mm, $P < 0.05$), adjustment for age rendered the differences insignificant. There were no differences in the relation of awake and sleeping systolic pressures to the left ventricular mass ($r = 0.36$ and 0.35, respectively, both $P < 0.005$) or to the carotid wall thickness ($r = 0.28$ and 0.29, respectively, both $P < 0.005$). When the 114 men and 69 women were considered separately, similar findings were obtained. When the 109 whites and 56 blacks (African-Americans and Afro-Caribbeans) were considered separately, there were no differences in left ventricular structure in either group, and differences in vascular structure were confined to the white subgroup.**

Conclusion **The lack of a normal nocturnal fall in blood pressure is not associated with an increase in left ventricular mass or in arterial disease independently of age. Age-related changes in carotid artery wall thickness and plaque among nondippers may reflect a contribution of an altered baroreceptor function to the lack of normal nocturnal and supine blood pressure decreases.**

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Introduction

Ambulatory blood pressure monitoring has documented variations in the diurnal pattern of blood pressure, the majority both of normotensive and of hypertensive individuals demonstrating a nocturnal fall (dipping) in blood pressure associated with sleep [1–3]. The absence of a normal nocturnal fall in blood pressure (nondipping) in hypertensive patients has been associated with an increase in left ventricular mass [4–6] and in frequency and complexity of ventricular ectopy [7] compared with those of hypertensive dippers [2–4]. Furthermore, in a small retrospective case–control study [8], a blunted nocturnal fall in blood pressure on baseline ambulatory monitoring was associated with subsequent major cardiac events for women, but not for men. In a subsequent, larger study by the same group [9], the relative risk of cardiovascular morbid events was increased for female, but not for male, nondippers, independently of age and echocardiographic left ventricular mass. In support of these findings, Schmieder *et al.* [10] reported that the left ventricular mass of female nondippers was significantly greater than that of female dippers but that this difference was not observed among men.

Vascular hypertrophy, which is inferred from an increase in minimum forearm vascular resistance, has also been

associated with a reduced nocturnal fall in blood pressure [6], as has an increase in urinary albumin excretion [11]. More recently, Muiesan *et al.* [12] reported a significant inverse relation between the change in systolic blood pressure from day to night and the presence of carotid plaque and the carotid intimal–medial thickness, although the latter difference did not appear to be independent of age and nocturnal systolic blood pressure. An increase in the cumulative pressure load has been thought to account for the observed differences between the cardiac and vascular structures of dippers and nondippers.

In contrast, other authors [13] have failed to detect any association between a blunted nocturnal fall in blood pressure and left ventricular hypertrophy or differences in forearm vascular resistance, and the correlations of daytime and night-time blood pressures with the left ventricular mass have been comparable [6,13]. Furthermore, Verdecchia *et al.* [9,14] found predominantly an increase in left ventricular mass in female, but not male, hypertensive nondippers. In preliminary analyses [15], we confirmed the well-documented improved relation of the ambulatory blood pressure compared with the casual blood pressure to the left ventricular mass [16], but failed to detect a similar improvement in the relation of the ambulatory blood pressure to the carotid artery diameter and intimal–medial thickness. The present analysis, of data from an expanded population, was designed to more thoroughly evaluate the strength of association of ambulatory blood pressure measures with cardiovascular structure and function, and to further examine the impact of a blunted nocturnal drop in blood pressure on hypertensive target organ damage involving the heart and the carotid artery as a representative conduit vessel.

Methods

Study population

The study population consisted of 183 consecutive subjects with hypertension who were being subjected to a protocol involving ambulatory blood pressure monitoring, echocardiography, and carotid ultrasonography at The New York Hospital–Cornell Medical Center. All of the patients were asymptomatic and free from clinical evidence of cardiovascular disease other than hypertension. Administration of medications to the 110 patients (60%) who had previously been administered pharmacologic antihypertensive therapy was stopped at least 3 weeks before the ambulatory monitoring and ultrasound studies. Of the subjects, 57% had participated in a worksite-based study described previously [17], and the remainder had been referred to the study protocol from the institution's Hypertension Center. The diagnosis of hypertension was based on the presence of a sustained elevation in blood pressure of $\geqslant 140$ mmHg systolic or 90 mmHg diastolic, or both, in individuals aged less than 65 years and of $\geqslant 160$ mmHg systolic or 90 mmHg diastolic, or both, in individuals aged 65 years or more. Blood specimens were obtained after the patients had fasted overnight, and serum lipids and electrolytes were measured using standard techniques. All of the studies were performed using protocols approved by the Institutional Review Board of Cornell University Medical College.

Ambulatory blood pressure

Ambulatory blood pressure recording was performed over a 24 h typical day (a work day or a day involving the patient's usual activities) for all subjects using a SpaceLabs 90207 (SpaceLabs Inc., Redmond, Washington, USA) monitor. As described previously [18], readings were obtained every 15 min during the day and every 30–60 min at night. Patients were instructed to note their activity in a diary. Blood pressure recordings were classified according to activity using custom-written software, and averaged to reflect actual awake and sleeping periods. To calculate the 24 h blood pressure, the variability among subjects in the duration of sleep and the less frequent pressure assessments during it were taken into account by weighting awake and sleeping pressure measurements for the proportion of the ambulatory recording they occupied. Blood pressure variability was assessed using the SD of awake and sleeping blood pressures and their coefficients of variation (SD of average blood pressure/average blood pressure). Because the 15–60 min intervals between measurements exceeded those used to calculate the very-low-frequency heart rate variability substantially, this is termed ultra-low-frequency blood pressure variability. Dipping was defined as a drop in sleeping systolic blood pressure of greater than 10% in comparison with the average awake systolic blood pressure. In secondary analyses, dipping was defined as a greater than 10% fall both in the systolic and in the diastolic blood pressure in order to provide comparability with one of the definitions used by Verdecchia *et al.* [4].

Echocardiography

All echocardiograms were recorded by a single highly experienced research technician using standard techniques. Strip-chart recordings were coded by the technician and measured by a single, blinded observer using a digitizing tablet. Left ventricular dimensions were measured according to American Society of Echocardiography recommendations [19]. The left ventricular mass was calculated using the formula $0.8(1.04[LVID_d + IVS_d + PWT_d]^3 - [LVID_d])^3 + 0.6$ g, where LVID is the left ventricular internal diameter, PWT is the posterior wall thickness, IVS is the interventricular septal thickness, and subscript d indicates end-diastole [20]. Whenever M-mode recordings were inadequate, ventricular measurements were obtained from the two-dimensional study according to American Society of Echocardiography recommendations [21]. The left ventricular mass was adjusted for the body surface area and for height$^{2.7}$ [22].

Left ventricular hypertrophy was categorized using three criteria: > 118 g/m^2 for men and > 108 g/m^2 for women [23]; > 125 g/m^2 both for men and for women [24]; and > 51 g/m$^{2.7}$ both for men and for women [22]. Left ventricular geometry was classified using the left ventricular mass index and relative wall thickness [25]. Left ventricular function was assessed by calculation of the fractional shortening, $(LVID_d - LVID_s)/LVID_d$, where subscript s indicates end-systole. Patients with valvular stenosis or more than mild valvular regurgitation detected by Doppler echocardiography were excluded from the study.

Carotid ultrasonography

Imaging of the right and left extracranial carotid arteries was performed by the research technician using a 7.0 or 7.5 MHz transducer with the patient supine with slight hyperextension of the neck. The arteries were scanned for the presence of discrete carotid atherosclerotic plaque [26]. An M-mode tracing of the distal left common carotid artery was recorded on videotape. Measurement of the intimal–medial thickness of the far wall at end-diastole and continuous tracing of the lumen–intima interface of the near and far walls were performed using a frame-grabber attached to a high-resolution monitor using previously described techniques [27]. Measurements were performed on several cycles and averaged. Wall-thickness and lumen measurements were never made at the level of a discrete plaque. The relative arterial wall thickness was calculated as 2 × wall thickness/end-diastolic diameter. The vascular strain was calculated according to the formula $(D_s - D_d)/D_d \times 100$, where D_s and D_d are the common carotid artery's peak-systolic (maximum) and end-diastolic (minimum) diameters, respectively. The supine brachial blood pressure was measured in triplicate by the technician upon termination of the ultrasound studies, using an appropriately sized cuff and mercury sphygmomanometer, and averaged.

Statistical methods

Values are expressed as means ± SD as the index of dispersion. Mean values for the dippers and nondippers were compared using Student's t test for independent samples. The impact of age on comparisons was taken into account by using analysis of covariance. Categorical variables were compared using χ^2 analysis. The relation of continuous variables was assessed using linear regression, whereas that of categorical variables was assessed using logistic regression analysis. The relative strength of correlations was compared using Fisher's z statistic.

Results

Study population

The study population (Table 1) consisted of 114 men and 69 women aged 55 ± 11 years (range 30–81). Of the subjects, 60% were white, 31% were African-American or Afro-Caribbean, 8% were Hispanic and 1% were Asian.

Table 1 **Clinical profiles of dippers and nondippers**

	Dippers (n = 104)	Nondippers (n = 79)	Significance
Age (years)	54 ± 10	57 ± 11	NS (0.06)
Sex (% male)	67	57	NS (0.1)
Race (% white)	66	51	NS (0.1)
BSA (m^2)	1.90 ± 0.21	1.86 ± 0.22	NS
BMI (kg/m^2)	26.7 ± 4.1	26.9 ± 3.9	NS
Smoking history (%)			NS
Current smoker	7	13	
Former smoker	35	37	
Cholesterol (mmol/l)	5.84 ± 1.09 (226 ± 42 mg/dl)	5.77 ± 1.03 (223 ± 40 mg/dl)	NS
HDL cholesterol (mmol/l)	1.29 ± 0.39 (50 ± 15 mg/dl)	1.42 ± 0.41 (55 ± 16 mg/dl)	$P < 0.05$
Glucose (mmol/l)	5.10 ± 1.33 (92 ± 24 mg/dl)	5.00 ± 2.11 (90 ± 38 mg/dl)	NS
Creatinine (μmol/l)	88.8 ± 17.9 (1.0 ± 0.2 mg/dl)	89.6 ± 21.0 (1.0 ± 0.2 mg/dl)	NS
Previous therapy (%)	60	61	NS

Values are expressed as means ± SD. BSA, body surface area; BMI, body mass index; HDL, high-density lipoprotein.

Of the patients, 104 (57%) were classified as dippers and 79 (43%) were classified as nondippers on the basis of their diurnal blood pressure patterns. The average nocturnal falls in systolic and diastolic blood pressures were 16 ± 4 and 20 ± 6%, respectively, in the dippers and 6 ± 4 and 10 ± 6%, respectively, in the nondippers ($P < 0.0005$ for both comparisons).

In comparison with the dippers, the nondippers were slightly older (57 ± 11 versus 54 ± 10 years, $P = 0.06$) and slightly less likely to be white (51 versus 66%, $P = 0.1$) and male (57 versus 67%, $P = 0.1$). Otherwise there were no differences in body size, smoking habits, and serum cholesterol, glucose, and creatinine levels. High-density lipoprotein cholesterol levels were slightly higher among the nondippers, possibly owing to the slight tendency for nondippers to be more likely to be women.

Blood pressure measurements

Average awake systolic and diastolic blood pressures were virtually identical in the dippers and nondippers (148/93 versus 149/93 mmHg, Table 2) and, therefore, sleeping blood pressures were significantly higher in the nondippers. The 24 h systolic, but not diastolic, blood pressure, was greater in the nondippers. The daytime blood pressure variability was greater in the nondippers, as assessed in terms both of the SD and of the coefficient of variation of the awake diastolic blood pressure, despite the identical nature of the average awake diastolic blood pressures. Although the SD of the sleeping systolic blood pressure was higher for the nondippers, this difference became statistically insignificant after we had controlled for their higher average sleeping systolic blood pressure (10.3 versus 10.2 mmHg). The supine blood pressure obtained at the end of the ultrasound studies (which required approximately 1 h in a quiet, darkened room) was significantly higher in the nondippers (156/93 versus 146/89 mmHg, $P < 0.005$). Differences between

Table 2 **Blood pressure and heart rate measurement results in dippers and nondippers**

	Dippers (n = 104)	Nondippers (n = 79)	Significance
Awake SBP (mmHg)	148 ± 15	149 ± 15	NS
Awake DBP (mmHg)	93 ± 11	93 ± 11	NS
Sleeping SBP (mmHg)	124 ± 15	141 ± 15	0.0005
Sleeping DBP (mmHg)	75 ± 11	83 ± 10	0.0005
24 h SBP (mmHg)	140 ± 14	147 ± 15	0.001
24 h DBP (mmHg)	87 ± 10	89 ± 10	NS
SD awake SBP (mmHg)	12.5 ± 3.2	13.0 ± 4.0	NS
SD awake DBP (mmHg)	9.1 ± 2.2	10.1 ± 2.6	0.005
SD sleeping SBP (mmHg)	9.6 ± 3.6	10.9 ± 4.3	0.05
SD sleeping DBP (mmHg)	8.2 ± 2.6	8.5 ± 3.1	NS
CV awake SBP (mmHg)	8.5 ± 2.1	8.7 ± 2.6	NS
CV awake DBP (mmHg)	9.9 ± 2.7	11.1 ± 3.2	0.01
CV sleeping BP (mmHg)	7.7 ± 2.8	7.7 ± 2.8	NS
CV sleeping DBP (mmHg)	11.1 ± 3.3	10.3 ± 3.6	NS
Supine SBP* (mmHg)	146 ± 17	156 ± 21	0.0005
Supine DBP* (mmHg)	89 ± 10	93 ± 11	0.005
Heart rate (beats/min)	69 ± 13	67 ± 12	NS

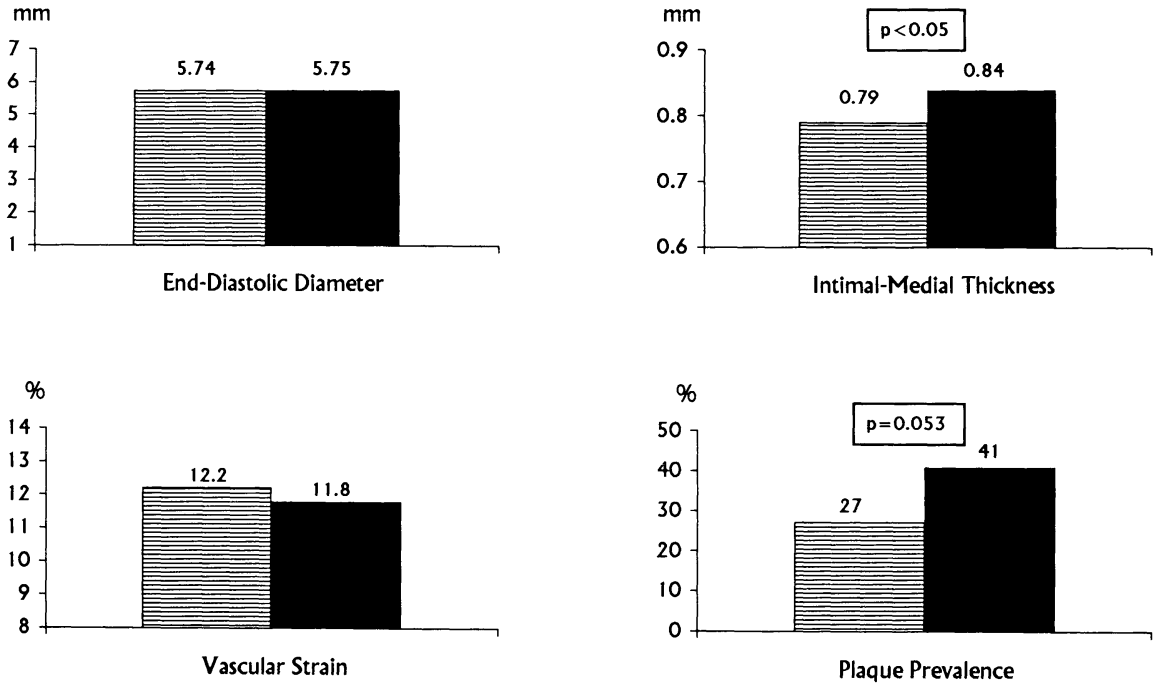
Values are expressed as means ± SD. DBP, diastolic blood pressure; SBP, systolic blood pressure; CV, coefficient of variation. *Measured upon completion of the ultrasound studies.

Table 3 **Left ventricular and common carotid artery structure and function in dippers and nondippers**

	Dippers (n = 104)	Nondippers (n = 79)	*P* value
Left ventricular			
Septum (cm)	0.99 ± 0.15	0.99 ± 0.15	NS
Posterior wall (cm)	0.91 ± 0.13	0.92 ± 0.12	NS
Diastolic diameter (cm)	4.99 ± 0.44	4.95 ± 0.51	NS
Relative wall thickness	0.37 ± 0.05	0.38 ± 0.06	NS
Mass (g)	172 ± 47	170 ± 46	NS
Mass index (g/m^2)	90.1 ± 20.5	91.1 ± 20.0	NS
Mass index ($g/m^{2.7}$)	40.4 ± 10.0	41.8 ± 9.9	NS
Fractional shortening (%)	38 ± 6	37 ± 5	NS
Abnormal geometry* (%)			
$> 118/108$ g/m^2	30	34	NS
$\geqslant 125$ g/m^2	14	16	NS
> 51 $g/m^{2.7}$	22	25	NS
Common carotid artery			
IMT (mm)	0.79 ± 0.17	0.84 ± 0.19	0.05
Diastolic diameter (mm)	5.74 ± 0.80	5.75 ± 0.69	NS
Relative wall thickness	0.28 ± 0.07	0.29 ± 0.06	NS
Strain (%)	12.2 ± 4.0	11.8 ± 3.4	NS
Plaque (%)	27	41	NS (0.053)

Values are expressed as means ± SD. IMT, intimal–medial thickness. *Eccentric hypertrophy, concentric hypertrophy, and concentric remodeling.

Fig. 1



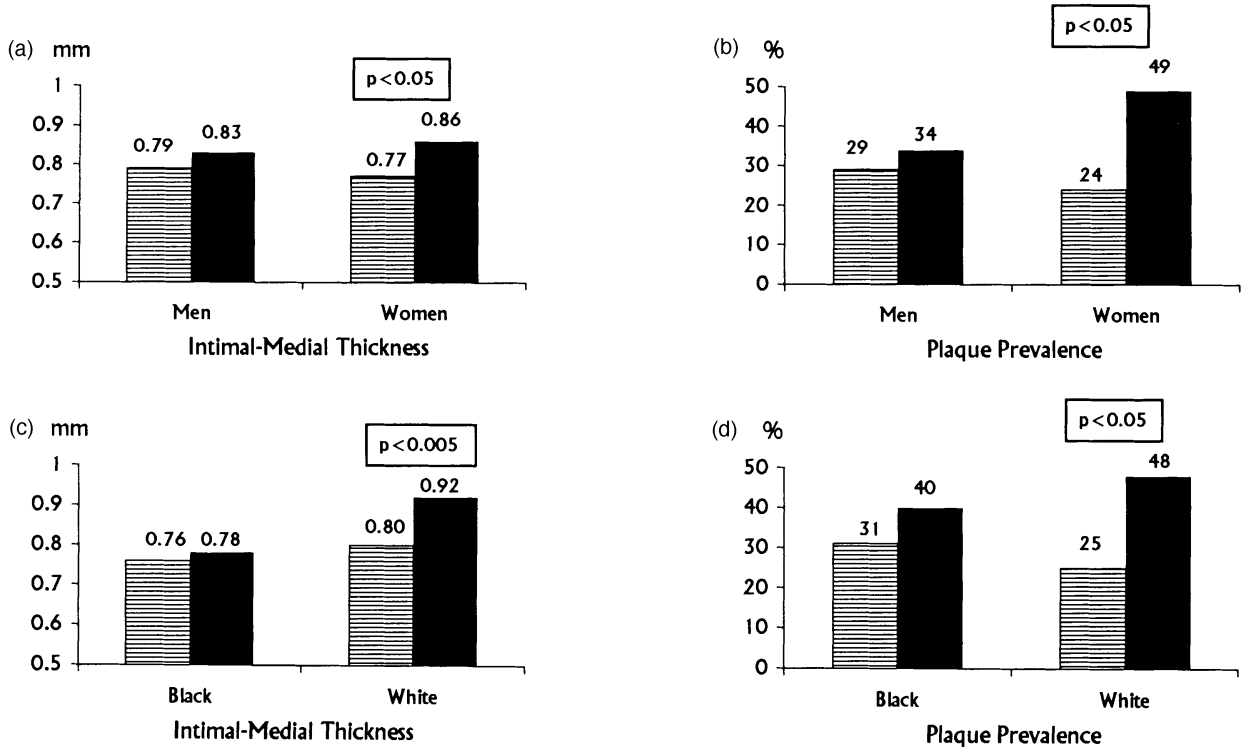
Comparison of common carotid artery structure and function in dippers (▤) versus that in nondippers (■). Differences in intimal–medial thickness and prevalence of plaque between the two groups were rendered insignificant after adjustment for age.

the daytime blood pressure variabilities and supine blood pressures persisted after analysis for covariance to take into account the tendency for nondippers to be slightly older.

Ventricular and vascular structure and function

Left ventricular absolute and relative wall thicknesses, chamber dimensions, mass, mass indexes, and function were similar in the dippers and nondippers (Table 3). The prevalence of abnormal patterns of left ventricular geometry (eccentric hypertrophy, concentric hypertrophy, and concentric remodeling) did not differ between the two groups, regardless of the definition used for left ventricular hypertrophy.

Fig. 2



Impact of sex (a, b) and race (c,d) on differences between dippers (▤) and nondippers (■) in vascular structure. All differences between female and white dippers and nondippers were rendered insignificant after adjustment for age, except for that in intimal–medial thickness, which remained significantly higher in white nondippers than it was in white dippers (0.90 versus 0.82 mm, $P < 0.05$).

Although the common carotid artery's intimal–medial thickness was greater in the nondippers, the difference became insignificant after we had controlled for age (0.83 versus 0.80 mm). The arterial lumenal diameter, relative wall thickness, and vascular strain were similar in members of the two groups. The prevalence of discrete atherosclerotic plaque tended to be higher among nondippers (41 versus 27%, $P = 0.053$); however, this trend weakened after we had controlled for age in logistic regression analysis ($P = 0.14$; Fig. 1).

Relation of casual and ambulatory blood pressures to cardiovascular structure

All measures of ambulatory and supine blood pressures were related significantly to the left ventricular mass (Table 4). There were no differences in the strengths of association of the ventricular mass with awake and sleeping blood pressures. The supine systolic blood pressure was significantly less strongly correlated to the left ventricular mass than were both awake blood pressures ($P < 0.05$), the sleeping diastolic blood pressure ($P < 0.01$), and the supine diastolic blood pressure ($P < 0.05$). Systolic but not diastolic blood pressures were related to the common carotid artery's wall thickness, there being no differences in the strengths of association with the carotid wall thickness among the awake, sleeping, and supine systolic blood pressures. The difference between the awake and the systolic sleeping blood pressure was not related to the left ventricular mass, carotid intimal–medial thickness, and presence of carotid plaque.

Impact of sex

When data for men and women were analyzed separately, results were not substantially different than those involving the entire population, although the levels of signifi-

Table 4 Univariate relations of ambulatory and supine blood pressures to cardiac and vascular structure

	Left ventricular mass	Carotid intimal–medial thickness
Awake SBP	0.36‡	0.28‡
Awake DBP	0.37‡	–0.12
Sleeping SBP	0.34‡	–0.02
Supine SBP*	0.21†	0.38‡
Supine DBP*	0.37‡	–0.03
Awake – sleeping SBP	0.03	–0.06

*Blood pressure measured upon completion of the ultrasound studies. SBP, systolic blood pressure; DBP, diastolic blood pressure. †$P < 0.005$, ‡$P < 0.0005$.

cance fell because of the smaller numbers. Supine blood pressures remained higher in nondippers than they were in dippers (151/94 versus 146/90 mmHg in men, $P < 0.05$ diastolic; 162/92 versus 146/87 mmHg in women, $P < 0.05$ diastolic and $P < 0.005$ systolic). There were no differences between dippers and nondippers in left ventricular structure (mass 187 versus 189 g in men; 141 versus 146 g in women). The carotid artery wall thickness (0.79 versus 0.83 mm) and prevalence of plaque (29 versus 34%) were similar among male dippers and nondippers, whereas female nondippers had a significantly greater carotid wall thickness (0.86 versus 0.77 mm, $P < 0.05$) and prevalence of discrete atheromas (49 versus 24%, $P < 0.05$) than did female dippers (Fig. 2). The differences in wall thickness and prevalence of plaque for women were eliminated after we controlled for age (61 years for nondippers versus 57 years for dippers).

Impact of race

When the entire population was considered, the black (n = 56) hypertensives (African-Americans and Afro-Caribbeans) were significantly younger than the white (n = 109) hypertensives (51 ± 9 versus 58 ± 11 years, $P < 0.0005$), had similar awake systolic blood pressures (150 ± 16 versus 148 ± 15 mmHg) but higher awake diastolic blood pressures (97 ± 10 versus 90 ± 10 mmHg, $P < 0.0005$) and higher sleeping blood pressures (135/83 versus 130/76 mmHg, $P < 0.05$ systolic and $P < 0.0005$ diastolic). The difference between the awake and the sleeping systolic blood pressure was lower for the blacks (9.5 ± 0.7 versus 12.4 ± 0.7%, $P = 0.01$), whereas the difference between the awake and the sleeping diastolic blood pressure was statistically similar (14.2 ± 0.8 versus 16.2 ± 0.8%, $P = 0.1$). The black hypertensives had a greater adjusted left ventricular mass (43.4 ± 11.2 versus 39.9 ± 9.1 g/m$^{2.7}$, $P < 0.05$) and relative wall thickness (0.38 ± 0.06 versus 0.36 ± 0.05, $P < 0.05$). Although the carotid intimal–medial thickness was larger in white hypertensives, the difference was eliminated when age had been taken into account.

To determine whether race influenced differences in cardiovascular structure between dippers and nondippers, subgroup analyses were performed. Black nondippers (n = 30) were comparable to black dippers (n = 26) in age, supine and awake blood pressures, blood pressure variability, and left ventricular and carotid structure and function. In contrast, white nondippers (n = 40) were older than white dippers (n = 69; 63 ± 11 versus 56 ± 10 years, $P < 0.005$) and had higher supine blood pressures even after adjustment for age (adjusted pressures 161/92 versus 148/87 mmHg, $P < 0.01$). There were no differences in left ventricular structure and function between white nondippers and dippers. The carotid intimal–medial thickness was greater in the nondippers, even after we had adjusted for age (0.90 versus 0.82 mm, $P < 0.05$). Although carotid plaques were more common among the white nondippers (48 versus 25%), the significance of this difference was eliminated when age was considered in logistic regression analysis (Fig. 3).

Impact of the definition of an abnormal nocturnal fall in blood pressure

When nondippers were defined as those with a less than 10% nocturnal drop both in the systolic and in the diastolic pressure, the 40 (21%) nondippers were significantly older than the 143 dippers (60 ± 10 versus 54 ± 10 years, $P < 0.005$). There were no differences in sex, racial distribution, and body size. The left ventricular mass index (89.9 ± 18.8 for dippers versus 95.4 ± 24.2 g/m^2 for nondippers) and prevalence of left ventricular hypertrophy were similar. Using this more restrictive definition, there were no longer differences between the two groups in carotid intimal–medial thickness (0.81 mm in members of both groups) and prevalence of plaque (31% among the dippers and 39% among the nondippers).

Impact of previous pharmacologic therapy

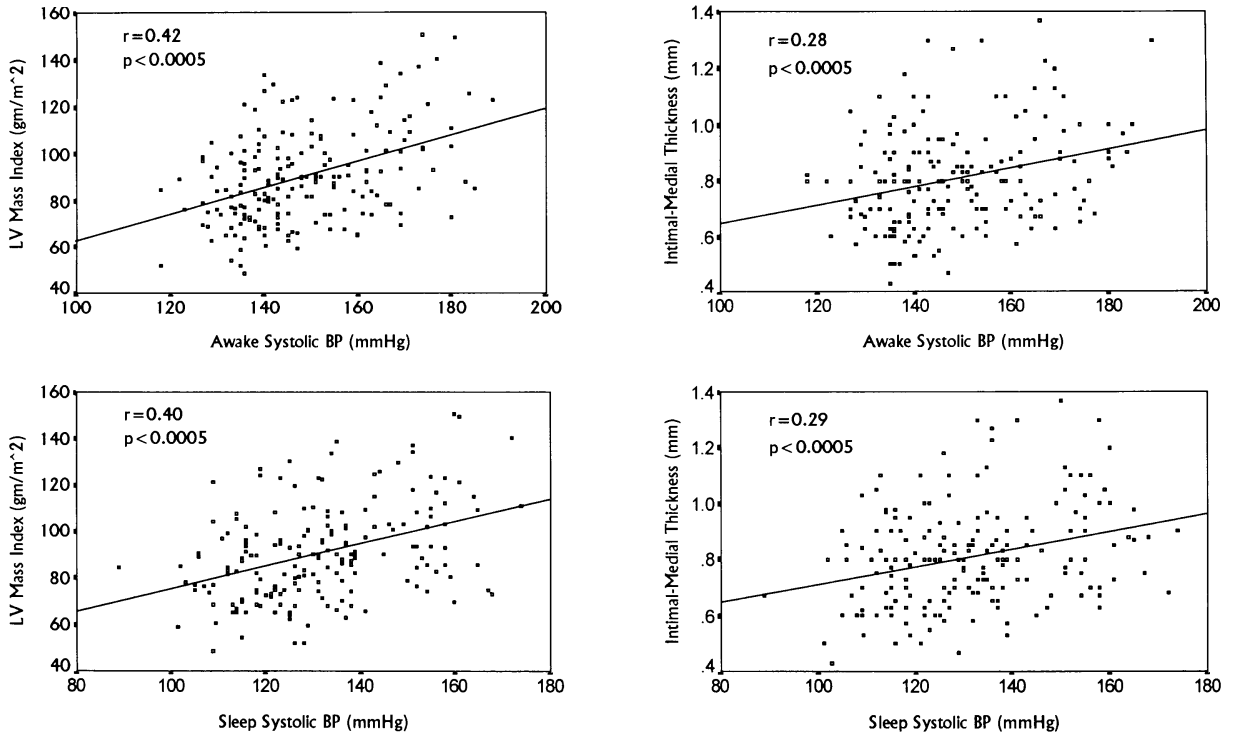
To determine whether previous pharmacologic therapy might have influenced findings, we performed analyses limited to those subjects who had never been administered pharmacologic antihypertensive therapy. The 42 dippers were similar to the 31 nondippers in age, sex, race, and all measures of left ventricular structure (left ventricular mass 168 ± 41 g in dippers and 167 ± 39 g in nondippers). The carotid intimal–medial thickness tended to be greater in members of the nondipper group (0.85 versus 0.76 mm, $P = 0.06$) and the relative vessel wall thickness was significantly greater in members of the nondipper group (0.30 versus 0.27, $P < 0.05$). Although discrete atherosclerotic plaques tended to be more prevalent among the nondippers (35 versus 24% among the dippers), the difference did not attain statistical significance.

Discussion

In the present study we found no difference in left ventricular size and function or prevalence of hypertrophy between hypertensive patients with and without a normal nocturnal fall in blood pressure. Our findings confirm those of Schulte *et al.* [13] concerning a small population of hypertensive men and women and those analyses of Verdecchia *et al.* [9,14] and Schmieder *et al.* [10] confined to men. Unlike the latter authors, we found no differences in left ventricular mass between female dippers and nondippers, despite the significantly greater supine blood pressures in member of the latter group. Furthermore, the relations of the awake and sleeping systolic and diastolic blood pressures to the left ventricular mass were virtually identical.

In contrast, a greater degree of vascular hypertrophy and atherosclerosis was present among the nondippers. These findings, however, appear to be attributable primarily to

Fig. 3



Relations of awake and sleeping systolic blood pressures (BP) to the left ventricular (LV) mass index and common carotid artery intimal–medial thickness.

age. Age is the strongest determinant of the carotid intimal–medial thickness both in normotensive and in hypertensive individuals [12,27,28] and, after we had controlled for age, differences in carotid wall thickness between dippers and nondippers were no longer significant. Age is also the most important determinant of carotid atherosclerosis [12,29]. It is of interest that nondippers were also older than dippers in previous reports of Verdecchia *et al.* [4,9] and among the men studied by Schmieder *et al.* [10]. Furthermore, the nocturnal fall in blood pressure has been shown to decrease with increasing age [30,31]. Unlike Muiesan *et al.* [12], we found no relation between the day–night difference in systolic blood pressure and the carotid intimal–medial thickness ($r = -0.06$, $P = 0.4$) or plaque.

Although the relation of target organ damage to an abnormal nocturnal fall in blood pressure has not been reported extensively, the conflicting findings in the existing literature may partially reflect several methodologic considerations. The fall in nocturnal blood pressure is caused primarily by sleep, presumably owing to sympathetic withdrawal [32]. Previous authors have usually defined night-time blood pressures somewhat arbitrarily as the blood pressure during the hours most likely to correspond to sleep, without referring to diaries specifying when subjects actually retired and awakened, as was done in the present study. Thus night-time blood pressures have previously been measured from 2000 h to 0600 h [4], 23.30 h to 0500 h [5], 2300 h to 0600 h [6], and 2200 h to 0600 h [8]. This use of fixed periods is primarily a consequence of manufacturers' software, and custom-written software is required to more precisely classify blood pressures according to activity. In a recent analysis comparing diary-determined sleeping blood pressures with blood pressures during differing fixed night-time periods, van Ittersum *et al.* [33] found that blood pressures during a 6 h fixed period from 0100 h to 0700 h correlated better to sleeping blood pressures than did longer periods, which overestimated sleeping systolic and diastolic pressures systematically.

Another methodologic issue concerns the definition of an abnormal fall in blood pressure. In their initial studies, Verdecchia *et al.* [4,9] defined dippers as those who had a greater than 10% nocturnal fall both in the systolic and in the diastolic blood pressures, whereas in a more recent analysis dippers were defined as those who had a greater than 10% drop either in the systolic or in the diastolic blood pressure [7,34]. Other definitions of normal nocturnal dipping have included a 10% drop in mean blood pressure [6,10], a night-time blood pressure less than the daytime blood pressure [5], and a fall of at least 10 mmHg in the systolic and 5 mmHg in the diastolic

blood pressure [11]. Before performing analyses, we chose a $\geq 10\%$ drop in systolic blood pressure as the criterion for normal dipping because of the substantially greater correlation of the systolic blood pressure to the left ventricular mass and carotid wall thickness [28] and because of the greater prognostic significance of the systolic blood pressure compared with the diastolic blood pressure [35]. Only two of our hypertensive patients had nocturnal drops in diastolic blood pressure $\leq 10\%$ in the absence of a comparable drop in systolic blood pressure, whereas less than one-half (38 versus 79) of those with a $< 10\%$ fall in nocturnal systolic blood pressure additionally had a $\leq 10\%$ fall in nocturnal diastolic blood pressure. Nevertheless, our results were not altered substantially by use of the earlier definition of dipping proposed by Verdecchia *et al.* [4]. In fact, use of this more restrictive definition completely eliminated differences in carotid wall thickening and atherosclerosis between dippers and nondippers.

A final methodologic issue concerns the possibility that the previously observed difference in left ventricular mass between dippers and nondippers is more a function of matching the two groups for daytime pressures, thereby, by definition, resulting in a higher cumulative 24 h pressure load in the nondippers [36]. Thus, when Verdecchia *et al.* [34] adjusted the left ventricular mass index for the mean night-time blood pressure, the mass actually became significantly lower in male nondippers than in male dippers and was comparable in female dippers and nondippers. When we performed similar analyses for our population, adjusting either for the sleeping systolic or for the sleeping diastolic blood pressure by analysis of covariance, the left ventricular mass likewise became significantly lower in the nondippers (159 versus 182 g after adjustment for the sleeping systolic blood pressure, $P < 0.005$). The lack of a difference in left ventricular mass between dippers and nondippers in the current study, despite the higher 24 h systolic blood pressure in the latter group and hence their higher cumulative pressure load, emphasizes the limited ability of the blood pressure to explain the variability in left ventricular mass (estimated r^2 of 12–15% in the present study). Furthermore, the magnitude of the nocturnal blood pressure difference might be minimal by definition (e.g. 11 versus 10% lower sleeping blood pressure in dippers and nondippers, respectively). In the current study, the nondippers had a 14% higher sleeping systolic blood pressure and an 11% higher sleeping diastolic blood pressure than did the dippers. The potentially greater impact of pressure-independent determinants of the left ventricular mass than of these small inter-group blood pressure differences would appear adequate to explain the lack of a greater left ventricular mass in the nondippers.

Examination of vascular changes associated with an abnormal nocturnal fall in blood pressure has been limited primarily to the resistance vessels. Among 68 hypertensive patients studied by Rizzoni *et al.* [6], those with a nocturnal mean blood pressure drop of less than 10% of the mean daytime blood pressure had a slight increase in minimum forearm vascular resistance (2.82 versus 2.13 U, $P < 0.05$). In contrast, Schulte *et al.* [13] found no relation of the forearm vascular resistance to the nocturnal fall in blood pressure. Finally, 24 h urinary albumin excretion was found to be significantly greater from nondippers than it was from dippers (42 versus 17.5 mg, $P < 0.001$) [11].

Although it is likely that the increased carotid intimal–medial thickness and higher prevalence of atherosclerotic plaques detected among nondippers in the present study are attributable to their slightly greater age, it is also possible that the abnormalities of arterial structure in the region of the carotid sinus baroreceptors are of pathogenetic significance in the blunted nocturnal fall in blood pressure. In accord with this possibility, the variabilities both of the awake diastolic blood pressure and of the supine systolic and diastolic blood pressures were greater for the nondippers despite their having similar average awake systolic and diastolic pressures, as would be expected if an increased vascular stiffness diminished the ability of baroreceptors to modulate swings in blood pressure. This hypothesis is supported by the observation by Kaplan *et al.* [37] that the reactivity of the blood pressure was related directly to the carotid intimal–medial thickness for men. Although it is not known whether an increased blood pressure variability predisposes subjects to atherosclerosis or, conversely, results from atherosclerosis, results from experimental studies support the former hypothesis [38].

Although an increase in ultra-low-frequency blood pressure variability in nondippers is consistent with attenuation of the normal buffering capacity of the carotid sinus baroreceptor, this does not explain the higher level of supine blood pressure in nondippers under highly standardized conditions upon completion of the ultrasound studies. One possible explanation is that greater venous tone, or volume expansion, could sustain higher night-time and daytime supine blood pressure levels and predispose subjects to greater blood pressure rises when intercurrent stimuli, such as local neurohormonal stimulation, cause arteriolar contraction. A more detailed analysis of differences in the response of the blood pressure to postural changes and their relation to abnormal vascular structure and regulation could be useful in clarifying these possibilities.

The hypothesis that differences in racial constitution of the population sample explain the differences between findings in the current study and those concerning other, exclusively white, populations was not supported by subgroup analyses. In the current study black hypertensives had higher awake and sleeping diastolic blood

pressures and less of a nocturnal drop in systolic blood pressure than did white hypertensives. Although higher night-time mean blood pressures in normotensive African-Americans [39] and Afro-Caribbeans [31] in comparison with those in white normotensives have been reported, the magnitude of the nocturnal fall did not differ between the races [31]. Despite black nondippers having significantly greater sleeping blood pressures than do black dippers (140/86 versus 129/80 mmHg, $P < 0.005$ systolic and $P < 0.05$ diastolic), we detected no differences between the two groups in cardiac and vascular structure. Comparison of the white dippers and nondippers yielded findings similar to those for the entire population. Thus, although a lesser difference in vascular structure was noted between black dippers and nondippers than between their white counterparts, race does not appear to account for differences in findings in the current study compared with those for other populations.

In conclusion, the present results confirm the improved relation of most ambulatory measures of blood pressure to the left ventricular mass compared with that of single casual readings but we detected no difference in the strength of relations for awake and sleeping blood pressures. Systolic but not diastolic blood pressures are related to the carotid wall thickness, and ambulatory awake, sleep and casual readings are comparable in their strength of relation. The increase in carotid thickening and atherosclerosis among non-dippers appears primarily related to their slightly older age, but may also result from or contribute to their increase in nocturnal and supine blood pressures and in variability of awake blood pressure.

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