Nocturnal Blood Pressure Fall on Ambulatory Monitoring in a Large International Database

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Abstract A wide range of definitions is used to distinguish subjects in whom blood pressure (BP) falls at night (dippers) from their counterparts (nondippers). In an attempt to standardize the definition of nondipping, we determined the nocturnal BP fall and night-day BP ratio by 24-hour ambulatory monitoring in 4765 normotensive and 2555 hypertensive subjects from 10 to 99 years old. In all subjects combined, the systolic/diastolic nocturnal fall and corresponding ratio averaged (±SD) −16.7±11.0/−13.6±8.1 mm Hg and 87.2±8.0%/83.1±9.6%, respectively. In normotensive subjects, the 95th percentiles were −0.3/−1.1 mm Hg for the nocturnal fall and 99.7%/98.3% for the night-day ratio. Both the fall and ratio showed a curvilinear correlation with age. The smallest fall and largest ratio were observed in older (≥70 years) subjects. A higher BP on conventional sphygmomanometry was associated with a larger systolic (partial r=.11) and diastolic (r=.12) nocturnal BP fall. The diastolic (r=.08) but not the systolic night-day ratio increased with higher conventional BP. The nocturnal BP fall was larger and the corresponding night-day ratio smaller in oscillometric (n=5884) than in auscultatory (n=1436) recordings, in males (n=3730) than in females (n=3590), and in Europe (n=4556) than in the other continents (n=2764). The distributions of the nocturnal BP fall and night-day ratio showed considerable overlap among normotensive and hypertensive subjects, but the overlap tended to be larger for the ratio than for the fall. Of all subjects, 3.2% had systolic and diastolic ratios of 100% or more. With adjustments applied for confounders, the probability of being a nondipper increased 2.8 times (95% confidence interval, 2.0-4.0) from 30 to 60 years and 5.7 times (4.4-7.4) from 60 to 80 years. The odds ratios were 1.0 (0.8-1.4) for males versus females, 1.6 (1.2-2.1) for subjects with definite hypertension versus normotensive subjects, 2.4 (1.2-4.7) for Asians (n=2213, 96% Japanese) versus inhabitants of the other continents, and 2.4 (1.5-3.8) for subjects examined with auscultatory versus oscillometric devices. In conclusion, the mathematical definition of nondipping, ie, having a night-day ratio of 100% or more for systolic and diastolic BPs, closely approximated the 95th percentiles of the night-day ratio in normotensive subjects. The ratio depends less on BP level than the nocturnal BP fall and is therefore to be preferred in the definition of dipping status. Notwithstanding the present findings, the reproducibility of nondipping and its prognostic significance need further clarification. (***Hypertension.* 1997;29:30-39.**)

Key Words • blood pressure monitoring, ambulatory • blood pressure • circadian rhythm

Ambulatory monitoring makes it possible to record blood pressure (BP) during habitual daily activities and sleep. Such ambulatory measurements are free of the white coat effect[1] and observer bias[2] and are therefore more reproducible than conventional BP readings.[3] Soon after the first intra-arterial recordings were performed in Oxford, it became apparent that BP was substantially lower during sleep than during daytime activities.[4]

In some individuals, BP does not fall at night.[5] These so-called nondippers may have more pronounced target-organ damage than their dipping counterparts and may be exposed to a higher incidence of cardiovascular complications.[6] However, a recent meta-analysis argued against the hypothesis that nighttime BP would be more closely associated with myocardial hypertrophy than daytime BP.[7] This controversy may originate, at least in part, from the wide range of definitions used to distinguish dippers from nondippers. In an attempt to derive a definition of nondipping, we analyzed an international database[8] to investigate the nocturnal BP fall and night-day BP ratio in normotensive and hypertensive subjects recruited in various parts of the world.

Received June 5, 1996; first decision July 8, 1996; revision accepted August 7, 1996.

A list of the participants in this research study and their affiliations appears at the end of this article.

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Methods

International Database

Experts in ambulatory BP monitoring were identified (1) from the list of attendants of the Second International Consensus Meeting on 24-Hour Ambulatory BP Measurement (Dublin, Ireland, September 23, 1991); (2) from computer searches of the English, French, and German literature from January 1980 until June 1991 using the Medical Literature Analysis and Retrieval System (MEDLARS); and (3) through contacts at international meetings. Thirty-three research groups were invited to make ambulatory BP recordings and relevant clinical information available for analysis. Twenty-four centers cooperated; six groups did not have suitable data; and three either did not reply or decided not to take part.

Unedited ambulatory BP recordings were available from 7860 individuals. Most studies from which these recordings had originated were described in peer-reviewed publications.[9-30] Of the 7860 subjects, 540 were excluded because there was no record of their conventional BP, because their ambulatory recording covered less than 20 hours, because fewer than 10 readings were available for the computation of average daytime BP, or because fewer than five readings were available for nighttime BP. The study group thus totaled 7320 subjects.

In agreement with current clinical practice, normotension and hypertension were defined on the basis of conventional BP measurements. Normotension was a BP not exceeding 140 mm Hg systolic and 90 mm Hg diastolic. Borderline hypertension was present if systolic pressure ranged from 141 through 159 mm Hg or diastolic pressure from 91 through 94 mm Hg. Definite hypertension was defined as a systolic pressure on conventional measurement of at least 160 mm Hg or a diastolic pressure of at least 95 mm Hg.

The subjects in the database were not treated with BP-lowering drugs or corticosteroids at the time of BP measurement. They were also not engaging in night work at the time of the recording. Subjects with hypertension had been examined on several occasions; however, the number of visits for which conventional BP readings could be made available for the present analysis varied from one to three. The conventional BP was the average of at least two readings in all subjects with borderline or definite hypertension. In contrast, some normotensive subjects had been examined only at a single occasion. Furthermore, in a few subjects, only one BP reading within the normotensive range had been deemed sufficient to exclude hypertension. If multiple conventional BP readings in various positions had been made available for analysis, only the first three measurements in the sitting position were averaged, because such readings were found to be available in the majority of subjects.

Ambulatory BP had been recorded noninvasively either with auscultatory devices (Accutracker II,[31] Del Mar Avionics Pressurometer P4,[32] Novacor DIASYS 200R,[33] Oxford Medilog,[34] SpaceLabs 5200,[35] and Takeda A&D TM-2420)[36] or oscillometric devices (SpaceLabs 90202[37] and 90207[37]) (for the addresses of the manufacturers, see Reference 38). Whenever ambulatory BP had been recorded simultaneously with both techniques (Colin Medical ABPM-630[39]), only the oscillometric measurements were used in the analysis.

Analysis of Ambulatory Recordings

All ambulatory recordings were processed by the same SAS programs (SAS Institute Inc) after conversion of the input data to a compatible database format with DBMS/Copy (Conceptual Software Inc). If ambulatory recordings were longer than 24 hours, only the first 24 hours was used for analysis. To avoid a potential source of bias, we did not edit the ambulatory recordings. The editing criteria[40] that were considered but actually not applied removed less than 0.5% of the readings without any effect on the findings.

Within-subject means of the ambulatory measurements were computed with weights according to the time interval between successive readings. Diaries marking the awake and sleeping periods were available in only 549 (7.5%) of the subjects. In keeping with current practice,[41] daytime and nighttime were therefore defined using short fixed-clocktime intervals, which ranged from 10 AM to 8 PM and from midnight to 6 AM, respectively. These definitions, which have been used in previous publications,[26] provide a more reliable estimate of awake and sleeping BPs than wide fixed-clocktime methods because they eliminate the transition periods in the morning and evening during which BP changes rapidly.[42]

Nocturnal BP fall was calculated by subtracting daytime from nighttime BP, such that a more negative difference indicated a larger BP fall at night. Night-day BP ratios were multiplied by 100, therefore expressing nighttime BP as a percentage of the daytime level. A ratio of 100% or higher signified the absence of a BP fall at night.

Other Statistical Methods

The null hypothesis that a group of values were normally distributed was tested by Shapiro-Wilks' statistic[43] if the sample size did not exceed 2000 and by Kolmogorov's D statistic for larger groups.[44] Skewness was evaluated by computation of the coefficient of skewness, ie, the third moment about the mean divided by the cube of the SD.[45] Its significance was read from the normal distribution after calculation of the error term as $\sqrt{(6/n)}$.[45]

Significant covariates of the dependent variables were traced by a stepwise linear regression procedure terminating when all regression coefficients were significant at 5%. In this analysis, conventional sphygmomanometry provided an estimate of BP level, which in mathematical terms was independent of the measurements obtained by ambulatory monitoring. Two dummy variables coded for residence in Europe, Asia, or elsewhere. Sex, the linear and squared terms of age, the technique of ambulatory monitoring, and body mass index were also considered for entry into the regression models. After identification of significant covariates, group means of the nocturnal BP fall and night-day BP ratios were compared by ANCOVA.

Exact confidence intervals for proportions were computed from the binomial distribution with StatXact software (CYTEL Software Corp). Finally, multiple logistic regression was used for identification of the factors influencing the probability of no decrease in BP at night.

Results

Description of the Study Population

Sex and Age Distribution

The number of subjects contributed by each investigator, the criteria by which the participants had been recruited, and their age and sex distributions are summarized in Table 1. The study population included 3730 males and 3590 females. Age (±SD) averaged 48±16 years (range, 10 to 99 years). The age distribution was similar in males and females: 2.5% were from 10 through 19 years old, 13.1% from 20 through 29, 14.6% from 30 through 39, 27.6% from 40 through 49, 17.9% from 50 through 59, 15.2% from 60 through 69, and 9.1% 70 years or older.

Conventional BP

The median number of visits for which conventional BP readings had been made available for analysis was two, and the median number of readings averaged was three. Conventional BP was the average of 2 readings in 2519 people, 3 readings in 3802, 4 readings in 262, 5 readings in 396, and 9 readings in 110 subjects. Only 1 BP reading had been obtained in 231 people, who all had a normal pressure on this single measurement.

A total of 4765 subjects (48.6% males) had a conventional BP within the normotensive range (Table 2). They were on average 45±15 years old. In 798 normotensive subjects (Staessen et al[26], Table 1), the conventional BP had been measured in the relaxed home environment. However, exclusion of the latter subjects did not alter the results. The database also comprised 2555 hypertensive subjects. Of these, 759 (61.1% males) had only a borderline elevation of their conventional systolic or diastolic BP, and 1796 (52.9% males) were definitely hypertensive (Table 2). Their ages averaged 53±18 and 51±15 years, respectively. The subjects with definite hypertension consisted of two partially overlapping groups, ie, 1338 subjects with systolic hypertension and 1326 with diastolic hypertension. Systolic and diastolic hypertension were present in 868 subjects; 470 had isolated systolic hypertension; and 458 showed isolated diastolic hypertension.

Ambulatory Measurements

The technique of ambulatory BP measurement was oscillometric in 5884 people (Table 1), auscultatory in 1356 (Table 1), and either auscultatory with oscillometric backup (SpaceLabs 5200, only the auscultatory readings were used) or oscillometric (SpaceLabs 90202) in 80 subjects (James et al[15], Table 1). In all 7320 subjects combined, the 24-hour recordings consisted of 49 (median) BP measurements. The 5th to 95th percentile interval ranged

TABLE 1. Subject Characteristics of the Study Population

Investigator	n	Subjects	Age, y	Men	N-NT, %	Device(s)	Visits	CBP	Day	Night
Baumgart et al[9]	103	S (r)	24 (20-29)	50	92	S_2, S_7	C 2 (6)	S (4)	40 (36-49)	14 (13-15)
De Gaudemaris et al[10]	158	E (v,d,n)	41 (15-75)	49	100	S_5, ND_2	S 1 (3)	S (3)	36 (22-42)	14 (7-22)
De Cort	352	P (v)	72 (59-97)	42	49	S_7	P 2 (12)	S (3)	40 (32-41)	14 (12-14)
Degaute et al[11]	45	E,S (v)	35 (19-72)	100	76	OM	C 1 (3)	S (3)	59 (43-106)	34 (30-66)
Enström et al[12]	159	C (r,d)	52 (40-64)	100	45	S_5	P 3 (1)	R (3)	32 (24-34)	13 (9-14)
Fagard et al[13]	37	P (v,h)	41 (26-56)	62	3	S_5	C 2 (10)	R (5)	37 (16-40)	13 (8-14)
Gosse et al[14]	231	E (v,n)	39 (21-74)	61	79	S_5, ND_2	S 1 (1)	S (1)	36 (26-40)	17 (11-19)
Gourlay	76	C (r)	47 (21-68)	59	64	A_{II}	S 1 (2)	S (2)	20 (7-24)	7 (6-8)
Hayashi et al[28]	311	? (v,d,n)	40 (15-86)	60	87	CM_6	S 3 (1)	S (3)	10 (10-10)	6 (6-6)
Imai et al[20]	429	C (r)	55 (12-72)	31	77	CM_6	S 1 (2)	S (2)	19 (15-22)	11 (8-12)
James et al[15]	80	E (v,d,n)	30 (21-50)	0	100	S_2, S_6	S 1 (5)	S (5)	34 (27-40)	12 (8-15)
Kawasaki	700	? (v,d)	54 (12-72)	57	78	CM_6	S 2 (6)	S (3)	17 (12-19)	9 (5-11)
Kuschnir	110	P (h)	55 (39-74)	45	0	T	C 3 (9)	S (9)	39 (37-40)	14 (12-14)
Kuwajima et al[21]	99	P (v)	78 (62-99)	56	43	CM_6	S 1 (3)	S (3)	16 (11-19)	11 (7-12)
Liu	26	E (v,d,n)	65 (44-76)	85	100	S_2	C 3 (1)	S (3)	20 (15-20)	12 (9-12)
Middeke and Schrader[27]	82	P (v)	39 (16-77)	46	50	S_2, S_7	C 1 (5)	S (5)	28 (18-42)	9 (6-10)
Mutti et al[16]	9	P (v)	43 (21-64)	44	100	S_7	C 1 (3)	S (3)	40 (30-41)	18 (11-18)
O'Brien et al[17]	896	E (v)	46 (29-51)	48	90	S_2, S_7	S 2 (2)	S (2)	19 (15-21)	12 (10-12)
O'Brien	938	P (v,h)	50 (16-81)	49	0	S_2, S_7	C 2 (2)	S (2)	20 (16-21)	12 (10-12)
Otsuka et al[18]	321	C (v,d,n)	38 (16-89)	41	90	CM_6	S 1 (3)	S (3)	34 (17-40)	21 (10-24)
Otsuka et al[19]	151	S (v,d,n)	20 (18-27)	0	99	CM_6	S 1 (3)	S (3)	36 (25-44)	23 (14-26)
Otsuka	122	P (v)	52 (15-81)	45	0	CM_6	C 1 (3)	S (3)	31 (14-40)	21 (9-24)
Palatini et al[22]	214	P (v)	31 (10-81)	86	17	S_5, D, T	C 1 (3)	S (3)	67 (50-87)	24 (17-28)
Schnall et al[23]	159	E (v)	43 (30-60)	89	99	S_5	S 2 (6)	S (4)	36 (23-41)	12 (7-15)
Staessen et al[26]	990	C (r)	49 (20-87)	49	77	S_2	H 2 (10)	S (3)	29 (21-32)	9 (7-9)
Staessen	36	P (v,h)	50 (19-69)	58	14	S_2, S_7	C 2 (10)	S (5)	38 (30-41)	12 (11-12)
Staessen et al[30]	161	E,S (v,d)	34 (19-62)	52	76	S_2, S_7	C 2 (10)	S (5)	40 (33-42)	12 (10-12)
Verdecchia et al[24]	145	E (v,d,n)	46 (16-91)	53	100	S_2, S_5, S_7	C 1 (3)	S (3)	38 (10-43)	23 (6-24)
Zhang et al[29]	54	E (v,d,n)	47 (22-76)	50	100	S_2	C 1 (2)	S (2)	29 (22-30)	18 (15-18)
Zachariah et al[25]	126	C (v,d,n)	49 (21-84)	44	95	D	S 2 (2)	S (2)	74 (50-85)	24 (16-29)

Subjects: S indicates student; C, community; E, employee (white- or blue-collar workers); and P, patient. Selection criteria are given in parentheses: d indicates people with concomitant disease excluded; h, borderline hypertension (140 mm Hg<systolic pressure (SBP)<160 mm Hg or 90 mm Hg<diastolic pressure (DBP)<95 mm Hg) or definite hypertension (SBP ≥160 mm Hg or DBP ≥95 mm Hg); n, normotensive (SBP ≤140 mm Hg and DBP ≤90 mm Hg); r, random sample; and v, volunteer. N-NT indicates percentage of subjects with normal blood pressure on conventional measurement. Devices: A_{II} indicates Accutracker II; CM_6, Collin Medical ABPM-630; D, Del Mar Avionics Pressurometer P4; OM, Oxford Medilog; ND_2, Novacor DIASYS 200R; S_5, S_2, and S_7, SpaceLabs 5200, 90202, and 90207, respectively; and T, Takeda A&D TM-2420. Visits indicates the number of visits (total number of conventional blood pressure readings between parentheses) available for analysis in each person. Letters indicate where blood pressure readings were obtained (S, special center; C, clinic; H, home; P, office of general practitioner). CBP indicates conventional blood pressure readings (R, recumbent; S, sitting); numbers in parentheses are numbers of readings averaged for the present analysis. Day, Night: Median number of ambulatory readings (5th to 95th percentile interval) averaged to calculate the daytime and nighttime blood pressure means. Age is shown as mean (range).

TABLE 2. Blood Pressure in Normotensive and Hypertensive Subjects According to the Technique of Ambulatory Recording

		Blood Pressure, mm Hg			
Subgroup		CBP	24-Hour	Day	Night
Classification according to CBP					
Normotension (n=4765)	SBP	119±12	116±10	122±11	106±11
	DBP	73±9	70±7	75±8	61±8
Borderline hypertension (n=759)	SBP	146±8	128±11	134±12	117±14
	DBP	83±9	76±8	81±9	68±9
Definite hypertension (n=1796)	SBP	169±18	142±16	148±17	129±19
	DBP	102±15	86±12	91±12	77±13
Technique of ambulatory recording					
Auscultatory (n=1356)	SBP	133±21	124±17	129±17	113±18
	DBP	83±14	77±11	82±12	69±12
Oscillometric (n=5884)	SBP	135±26	123±16	129±17	113±17
	DBP	81±17	74±11	79±11	65±11
Whole database					
All subjects (n=7320)	SBP	134±25	123±16	129±17	113±17
	DBP	81±16	75±11	79±12	66±12

CBP indicates conventional blood pressure; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Values are mean±SD.

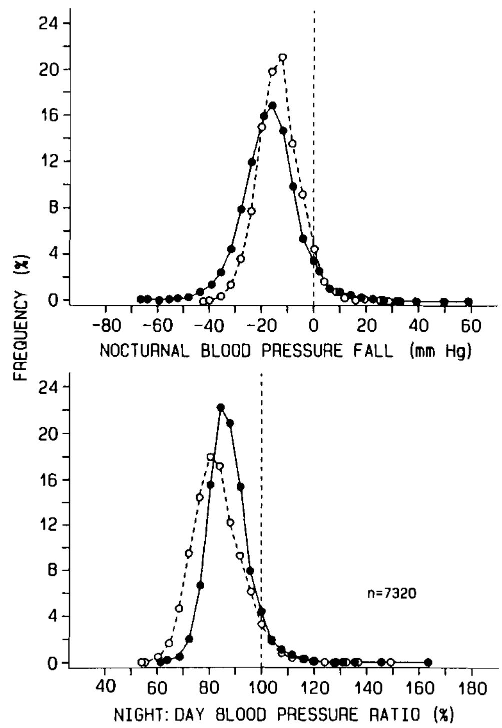

FIG 1. Distributions of nocturnal blood pressure fall (top) and night-day blood pressure ratio (bottom) in 7320 subjects. Frequency histograms were calculated for systolic (●) and diastolic (O) pressures separately with the use of 4 mm Hg or 4% intervals.

from 24 to 116 readings. The daytime BP averaged 129±17 mm Hg systolic and 79±12 mm Hg diastolic and the nighttime BP, 113±17 and 66±12 mm Hg. Pulse rate was determined from the ambulatory recordings in 6974 subjects. During the daytime, it averaged 79±10 beats per minute and at night, 63±9.

In general, the ambulatory pressure level increased with higher conventional BP (Table 2). Subjects monitored with auscultatory devices, compared with their counterparts examined with oscillometric machines, had lower ($P<.001$) systolic conventional pressures but higher ($P<.001$) diastolic pressures on conventional and ambulatory measurement. The interval between the ambulatory readings was on average shorter in the auscultatory than in the oscillometric recordings (20±10 versus 30±10 minutes, $P<.001$).

Nocturnal BP Patterns

In all subjects combined, the nocturnal BP fall averaged −16.7±11.0 mm Hg systolic and −13.6±8.1 mm Hg diastolic. The corresponding night-day ratios were 87.2±8.0% and 83.1±9.6%, respectively. The distributions of these measurements (Fig 1) deviated from normality ($P<.001$). The coefficients of skewness were (SE: ±0.029) 0.332, 0.177, 0.886, and 0.577 ($P<.001$ for all), respectively. In the normotensive subjects, the distributions of the nocturnal BP fall and night-day ratios tended to deviate from normality, but this was not the case in subjects with borderline or definite hypertension (Table 3).

For both systolic and diastolic BPs, the distributions of the nocturnal fall and night-day ratios showed considerable overlap among normotensive subjects and those with definite hypertension (Fig 2). The 95th percentiles in the former were −0.3 and −1.1 mm Hg and 99.7% and 98.3%, respectively (Table 3). Of the subjects with definite hypertension on conventional measurement, 9.4%, 8.4%, 10.2%, and 7.5% exceeded these thresholds. Conversely, the 5th percentiles in the normotensive population were −30.2 and −25.2 mm Hg and 76.6% and 68.7%, respectively. Values lower than these thresholds were observed in 19.4%, 12.1%, 9.3%, and 4.5% of the hypertensive subjects. Thus, the overlap between normotensive and hypertensive subjects tended to be greater for the ratios than for the nocturnal falls in BP expressed in millimeters of mercury (Fig 2).

Determinants of the Nocturnal BP Pattern

Anthropometric Characteristics

The nocturnal BP fall and night-day BP ratio showed a curvilinear correlation with age (Fig 3). These associations

TABLE 3. Distributions of Nocturnal Blood Pressure Fall and Night-Day Blood Pressure Ratio in Normotensive and Hypertensive Subjects

Subgroup		Mean±SD	P_5	P_{50}	P_{95}	*P*
Nocturnal blood pressure fall, mm Hg						
Normotension (n=4765)	SBP	15.9±9.4	-30.2	16.3	−0.3	.038
	DBP	13.5±7.4	-25.2	13.6	−1.1	.031
Borderline hypertension (n=759)	SBP	17.0±12.1	-34.8	17.7	3.3	.975
	DBP	13.0±8.8	-26.7	13.4	0.8	.988
Definite hypertension (n=1796)	SBP	18.5±13.9	-40.1	19.1	4.5	.982
	DBP	14.0±9.4	-29.8	14.2	1.4	.987
All subjects (n=7320)	SBP	16.7±11.0	-33.9	16.8	1.3	.041
	DBP	13.6±8.1	-26.6	13.7	−0.2	.027
Night-day blood pressure ratio, %						
Normotension (n=4765)	SBP	87.1±7.4	76.6	86.5	99.7	.051
	DBP	82.3±9.2	68.7	81.6	98.3	.047
Borderline hypertension (n=759)	SBP	87.5±8.7	75.7	86.6	102.5	.958
	DBP	84.3±10.3	69.5	83.0	101.2	.971
Definite hypertension (n=1796)	SBP	87.6±9.1	74.1	86.7	103.0	.974
	DBP	84.9±10.0	69.1	84.4	101.7	.981
All subjects (n=7320)	SBP	87.2±8.0	75.8	86.5	101.1	.048
	DBP	83.1±9.6	68.7	82.3	99.8	.041

P_5, P_{50}, and P_{95} indicate 5th, 50th (median), and 95th percentiles, respectively; SBP, systolic blood pressure; and DBP, diastolic blood pressure. $P<.05$ indicates significant departure from normality.

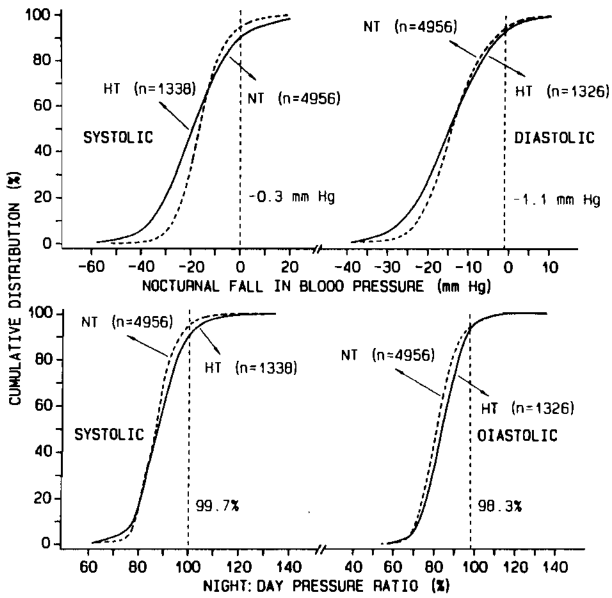

FIG 2. Cumulative distributions of nocturnal pressure fall (top) and night-day ratios (bottom) for systolic (left) and diastolic (right) pressures in normotensive (NT, unbroken lines) and hypertensive (HT, dotted lines) subjects. Subjects with borderline hypertension (n=759) were excluded from this analysis.

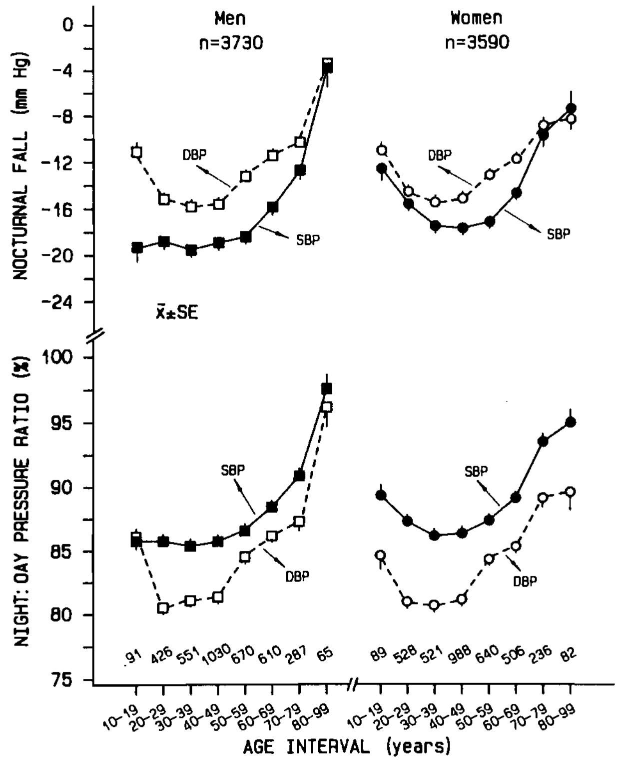

FIG 3. Nocturnal pressure fall (top) and night-day ratios (bottom) for systolic (SBP, filled symbols) and diastolic (DBP, open symbols) blood pressures in 10-year age classes in 3730 males (left) and 3590 females (right). For each sex and age group, the number of subjects contributing to the mean (±SE) is given.

were mirrored by the corresponding relationships between age and the nocturnal decline in pulse rate, which averaged −15.5±9.5 beats per minute in males (n=3519) and −15.2 ±8.6 in females (n=3455). In the eight age classes of males shown in Fig 3, the nocturnal decline in pulse rate (beats per minute) averaged −17.6 (n=87), −18.1 (n=414), −16.5 (n=482), −15.5 (n=970), −13.9 (n=613), −15.6 (n=601), −13.8 (n=287), and −8.4 (n=65), respectively; the corresponding values in females were −19.9 (n=89), −17.3 (n=475), −17.0 (n=482), −15.2 (n=968), −14.4 (n=623), −14.2 (n=500), −10.7 (n=236), and −10.5 (n=82).

After adjustment for age and other significant covariates—ie, BP level on conventional sphygmomanometry, continent of residence, and the technique of ambulatory measurement—the nocturnal BP fall was greater in males than females. In keeping with these findings, the systolic night-day ratio was also slightly smaller in males (Table 4).

Body mass index was available in 5303 subjects and averaged 24.7±4.1 kg/m^2 (range, 14.0 to 52.7). Body mass index correlated with the nocturnal fall in diastolic pressure (slope±SE [b]: 0.060±0.028 mm Hg [kg/m^2]$^{-1}$) and with night-day ratios for systolic (b: 0.050±0.027 [kg/m^2]$^{-1}$) and diastolic (b: 0.113±0.033 [kg/m^2]$^{-1}$) BPs. Accounting for body mass index in 5303 subjects reduced

TABLE 4. Nocturnal Blood Pressure Fall and Night-Day Blood Pressure Ratio in Various Subgroups

		Nocturnal Fall, mm Hg		Night-Day Ratio, %	
Subgroup	**n**	**SBP**	**DBP**	**SBP**	**DBP**
Sex					
Males	3730	−16.7±0.2 (A)	−12.3±0.2 (A)	87.5±0.2 (A)	84.8±0.2 (A)
Females	3590	−15.1±0.2 (B)	−11.9±0.2 (B)	88.3±0.2 (B)	84.9±0.2 (A)
Blood pressure					
Normotension	4765	−14.8±0.2 (A)	−12.0±0.1 (A,C)	87.9±0.1 (A)	84.2±0.2 (A)
Borderline hypertension	759	−17.4±0.4 (B)	−12.8±0.3 (B)	87.2±0.3 (B)	85.2±0.4 (A)
Definite hypertension	1796	−17.8±0.3 (B)	−12.3±0.2 (B,C)	88.2±0.2 (A)	86.9±0.2 (B)
Residence					
Europe	4556	−16.7±0.2 (A)	−13.5±0.1 (A)	87.1±0.1 (A)	83.4±0.2 (A)
Asia	2213	−15.7±0.3 (B)	−10.0±0.2 (B)	87.9±0.2 (B)	87.5±0.3 (B)
Other	551	−15.3±0.5 (B)	−12.9±0.4 (A)	88.8±0.4 (C)	83.7±0.4 (A)
Recording technique					
Auscultatory	1436	−15.3±0.3 (A)	−10.2±0.2 (A)	88.2±0.2 (A)	87.3±0.3 (A)
Oscillometric	5884	−16.5±0.2 (B)	−14.0±0.2 (B)	87.6±0.2 (B)	82.4±0.2 (B)

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Values are mean±SE adjusted for significant covariates. Dissimilar letters indicate significant ($P \leq .05$) differences.

TABLE 5. Probability of Being a Nondipper in Various Subgroups

Subgroup	n	SBP ND	SBP %*	DBP ND	DBP %*	Both ND	Both %*
Sex							
Males	3730	219	5.9 (5.1-6.7)	201	5.4 (4.7-6.2)	127	3.4 (2.8-4.0)
Females	3590	225	6.3 (5.5-7.1)	149	4.2 (3.5-4.9)	106	3.0 (2.4-3.6)
Both	7320	444	6.1 (5.5-6.6)	350	4.8 (4.3-5.3)	233	3.2 (2.8-3.6)
Blood pressure							
Normotension	4765	225	4.7 (4.1-5.4)	179	3.8 (3.2-4.3)	121	2.5 (2.1-3.0)
Borderline hypertension	759	62	8.2 (6.3-10.4)	49	6.5 (4.8-8.4)	33	4.4 (3.0-6.1)
Definite hypertension	1796	157	8.7 (7.5-10.1)	122	6.8 (5.7-8.1)	79	4.4 (3.5-5.5)
Residence							
Europe	4556	223	4.9 (4.3-5.6)	186	4.1 (3.5-4.7)	112	2.5 (2.0-3.0)
Asia	2213	166	7.5 (6.4-8.7)	123	5.6 (4.6-6.6)	101	4.6 (3.7-5.5)
Other	551	55	10.0 (7.6-12.8)	41	7.4 (5.4-10.0)	20	3.6 (2.2-5.6)
Recording technique							
Auscultatory	1436	97	6.8 (5.5-8.2)	101	7.0 (5.8-8.5)	47	3.3 (2.4-4.3)
Oscillometric	5884	347	5.9 (5.3-6.5)	249	4.2 (3.7-4.8)	186	3.2 (2.7-3.6)

n indicates total number of subjects in group; ND, number of nondipping subjects in defined subgroups. A nondipping pattern was defined as a night-day ratio equal to 100% either for systolic pressure (SBP), for diastolic pressure (DBP), or for both.

*Probability expressed as percent with 95% confidence interval between parentheses.

the sex difference (Table 4) in the nocturnal fall of diastolic pressure to a nonsignificant level.

Normotension Versus Hypertension

In multiple regression analysis, the BP level on conventional sphygmomanometry was significantly and negatively correlated with systolic (b: -0.071 ± 0.005 mm Hg [mm Hg]$^{-1}$) and diastolic (b: -0.027 ± 0.006 mm Hg [mm Hg]$^{-1}$) BP changes at night, of which 1.3% and 1.4%, respectively, were explained in this way. Thus, a higher conventional BP was associated with a larger nocturnal BP fall, if the latter was expressed on an absolute scale, ie, in millimeters of mercury. Furthermore, the height of the conventional BP correlated positively with the night-day ratio of diastolic (b: 0.056 ± 0.007% [mm Hg]$^{-1}$) but not systolic BP. Thus, after normalization of the nighttime for the daytime diastolic pressure, a higher conventional diastolic pressure was still associated with a higher night-day ratio, ie, a lesser nocturnal fall in diastolic pressure. However, the latter association was weak, accounting for only 0.6% of the variance of the diastolic night-day ratio.

After adjustment for sex, age, continent of residence, and the technique of ambulatory monitoring, hypertensive subjects tended to have a larger nocturnal BP fall than normotensive subjects (Table 4). In addition, the night-day ratio for diastolic pressure was significantly greater in subjects with definite hypertension than in the normotensive group.

Residence

Of the 7320 subjects, 3799 lived in Northern Europe (Belgium, 1621; Germany, 185; Ireland, 1834; Sweden, 159), 757 in Southern Europe (France, 389; Italy, 368), 2213 in Asia (Japan, 2133; People's Republic of China, 80), and 551 in other continents (Argentina, 110; Australia, 76; United States, 365). With adjustments for significant covariates applied, subjects living in Northern and Southern Europe showed the same nocturnal BP fall and similar night-day ratios for systolic and diastolic BPs. They were therefore pooled in the analysis. The day-night differences and night-day ratios were compatible with larger ($P<.001$ for all) nocturnal decreases in systolic and diastolic BPs in Europe than in the other continents (Table 4).

Technique of Ambulatory Recording

After adjustment for significant covariates, the nocturnal BP fall was smaller and night-day ratios larger in subjects whose BP had been recorded with an auscultatory rather than oscillometric technique (Table 4).

Further adjustment for body mass index in a group of 5303 subjects removed the systolic differences between the auscultatory (n=1090) and oscillometric (n=4213) techniques in the nocturnal BP fall (-16.4 ± 0.4 versus -16.8 ± 0.3 mm Hg, $P=.33$) and night-day ratio (87.4 ± 0.3% versus 87.5 ± 0.2%, $P=.87$). However, with similar adjustments applied, the diastolic differences between both types of measurement persisted in both the nocturnal BP fall (-11.2 ± 0.3 versus -14.6 ± 0.2 mm Hg, $P<.001$) and night-day ratio (86.1 ± 0.3% versus 81.9 ± 0.2%, $P<.001$).

Nondippers Versus Dippers

Nondipping BP profiles were defined as showing a night-day BP ratio of 100% or higher because this threshold corresponds mathematically with a nighttime BP equal to or higher than the daytime pressure. In the present analysis, this threshold approximated to the 95th percentiles of the night-day BP ratios in the normotensive subjects (Table 3, Fig 2).

In the whole database, 444 subjects (6.1%) showed a nondipping pattern for systolic pressure and 350 (4.8%) for diastolic pressure. In general, a nondipping pattern tended to be more often observed for systolic than for diastolic BP (Table 5). In view of the large variability in the diurnal BP profiles, nondippers were further characterized as subjects showing a nondipping profile for systolic as well as diastolic BP. Nondipping for both systolic and diastolic BPs was present in only 233 subjects (3.2%).

Below age 30 there were 1.6% nondipping subjects, 0.7% from 30 through 39, 1.3% from 40 through 49, 2.8% from 50 through 59, 4.9% from 60 through 69, 11.1% from 70 through 79, and 21.1% aged 80 or above. With adjustments applied for sex, the presence of definite hypertension on conventional sphygmomanometry, the technique of ambulatory measurement, and the continent of residence, the probability of being a nondipper was significantly correlated with both the linear (P=.005) and quadratic (P<.001) terms of age. The logistic model showed that with adjustments applied for all covariates, the odds ratio associated with age increasing from 20 to 30 years was only 0.93 (95% confidence interval [CI], 0.72-1.18). However, with similar adjustments, the probability of being a nondipper increased 2.81 times (CI, 1.99-3.98) from 30 to 60 years and 5.69 times (CI, 4.38-7.39) from 60 to 80 years.

After adjustment for all significant covariates, the odds of being a nondipper were the same in males and females (odds ratio, 1.03; CI, 0.78-1.35; P=.83). The odds were 1.56 times (CI, 1.16-2.09; P=.004) higher in subjects with definite hypertension as opposed to normotensive subjects. The odds ratios for Asians and Europeans, each time versus the remainder of the database, were 2.39 (CI, 1.20-4.74; P=.01) and 1.11 (CI, 0.61-2.03), respectively. Participants examined with auscultatory instead of oscillometric devices had a 2.44 (CI, 1.54-3.85; P<.001) higher probability of being a nondipper. All these estimates were adjusted for the other explanatory variables in the analysis.

Discussion

There is a growing interest in the hypothesis that hypertensive individuals with a nondipping nocturnal profile may have a worse prognosis than the majority of hypertensive and normotensive subjects who do show a fall in BP at night. Verdecchia et al[6] defined nondipping as a reduction in average systolic and diastolic BP values by 10% from day (6 AM to 10 PM) to night (10 PM to 6 AM). After adjustment for sex, age, diabetes, and echocardiographic left ventricular hypertrophy, nondipping women with hypertension on ambulatory monitoring experienced a higher cardiovascular morbidity than their dipping counterparts. However, this was not the case in nondipping men with a similarly elevated BP.[6] Furthermore, a meta-analysis of 19 studies,[7] involving 1223 participants, indicated that the weighted correlation coefficient for the relationship between left ventricular mass (index) and systolic nighttime BP (r=.44; CI, 0.39-0.48) was not significantly different from the correlation with systolic daytime BP (r=.48; CI, 0.44-0.52). The corresponding correlation coefficients for diastolic pressure both averaged .37. In half of the eight studies in which the association between left ventricular mass (index) and the day-night difference in BP was analyzed, investigators found no significant relationship between those variables; in the others, the variance of the mass (index) that could be explained by the BP difference was 15% at the most.

The first step in trying to clarify the discordant findings in the literature is to standardize the definitions of dipping versus nondipping and to determine the magnitude of the nocturnal BP fall that constitutes dipping. In addition, uniform definitions of day and night would help in comparing the various studies. In 18 studies in normotensive subjects, the night-day ratio averaged 87% systolic and 83% diastolic, with ranges across the studies from 79% to 92% and from 75% to 90%, respectively.[46] However, in these studies, disparate definitions of day and night were used.[46] In the present study, these intervals were fixed. In keeping with recent findings,[41,42] a short nighttime period of 6 hours was used. This approach provides an accurate estimate of BP during sleep in subjects who rest at night, whereas wide fixed-clocktime intervals may overestimate the true sleeping BP.[41,42] With use of these uniform definitions, the night-day ratios in the normotensive subjects of the database averaged 88% systolic and 84% diastolic (Table 4). These values were almost identical to the pooled estimates in the earlier meta-analysis.[46] Furthermore, in a Belgian population study (n=1057)[26] in which the participants represented nearly 70% of a random population sample, the nocturnal BP fall averaged 17.1±9.1 mm Hg systolic and 15.0±6.9 mm Hg diastolic. The night-day ratios were 86±7% and 81±8%, respectively. These averages approximate the values obtained in all 7320 subjects combined (Table 3) and suggest that the present findings are not particularly biased by the selection of the subjects in the various subsamples.

In the present analysis, the nocturnal BP fall increased by 1.8 mm Hg systolic and 0.4 mm Hg diastolic for a 1-SD increment in the BP on conventional sphygmomanometry (25/16 mm Hg). Accordingly, in absolute terms, ie, in millimeters of mercury, the nocturnal BP fall was larger in hypertensive than normotensive subjects (Table 4). In contrast, the systolic night-day ratio was unrelated to the BP level on sphygmomanometric measurement, and the diastolic ratio increased by only 1% for a 1-SD rise (16 mm Hg) in the diastolic conventional BP. The latter association signified that after normalization for daytime BP level, a higher conventional BP was still associated with a smaller nocturnal decrease in diastolic pressure. Because in most subjects the etiologic diagnosis of hypertension had been established only on clinical grounds, the database may have incorporated some cases of secondary hypertension. The inclusion of such subjects may partially explain why for diastolic pressure, a positive, albeit weak, correlation between the night-day ratio and BP level on conventional sphygmomanometry persisted. Indeed, such subjects usually have a considerably elevated BP, while their diurnal profile is often flattened or even inverted.[27] On the other hand, in keeping with the present findings on systolic pressure, James et al[47] reported that the percentage change to sleep pressure from the average awake value did not depend on the BP level in the office.

The overlap in the distributions between the normotensive subjects and subjects with definite hypertension tended to be smaller for the night-day ratios than for the absolute BP changes at night (Fig 2). The observation that the ratios depended less on BP level and the fact that they were normalized for daytime BP level may be considered as arguments in favor of the use of ratios rather than absolute changes in BP. Indeed, in distinguishing between dippers and nondippers, preference should be given to an index, which is not influenced by other factors, such as the height of the BP.

Several investigators found a decline in the daytime BP level by 10% to be a practical threshold in defining dippers as opposed to nondippers.[6] This threshold, equivalent to a night-day ratio of 90%, coincided with the 70th and 82nd percentiles of the systolic and diastolic BP ratios in the normotensive subjects and with the 68th and 78th percentiles in all 7320 subjects (Fig 2). Accordingly, had the 90% threshold been applied to systolic pressure alone, as many as 31.8% of all subjects in the database should have been labeled as nondippers. This proportion would have been 22.0% if only diastolic BP had been considered and 18.2% if systolic and diastolic pressures had been combined.

of ambulatory measurement, and the continent of residence, the probability of being a nondipper was significantly correlated with both the linear (P=.005) and quadratic (P<.001) terms of age. The logistic model showed that with adjustments applied for all covariates, the odds ratio associated with age increasing from 20 to 30 years was only 0.93 (95% confidence interval [CI], 0.72-1.18). However, with similar adjustments, the probability of being a nondipper increased 2.81 times (CI, 1.99-3.98) from 30 to 60 years and 5.69 times (CI, 4.38-7.39) from 60 to 80 years.

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The present findings suggest that a ratio equal to or higher than unity (100%) may constitute a reasonable alternative to the 90% criterion. The 100% threshold approximated the 95th percentiles of the distributions in the normotensive subjects. In mathematical terms, this limit also represents the literal translation of a nighttime BP equal to or higher than the daytime level. Because BP through the day is characterized by large variability, a few extreme values may easily shift a subject's classification, if dipping status were to be based on either systolic or diastolic BP alone. The distinct use of both pressures also jeopardizes the internal consistency of classifications within studies, because subjects may be systolic nondippers and diastolic dippers, or vice versa. Verdecchia et al[6] therefore quite rightly considered systolic and diastolic BPs in conjunction. In the present study, we also adhered to this more stringent approach. As expected, it reduced the prevalence of nondipping from 6.1% or 4.8% for systolic or diastolic pressure, considered separately, to 3.2% for both pressures combined (Table 5). These findings are in close agreement with a report by Palatini et al,[22] who found that the prevalence of nondipping was 3.3% in 728 subjects, of whom 661 were hypertensive.

The reproducibility of the dipping status, as defined in the present study, obviously needs further clarification. In the database, only one recording was available per subject, which precluded reproducibility studies. However, in several other reports,[3,48] the reproducibility of the nocturnal BP fall was not high. In a Belgian population study,[3] regression-to-the-mean was observed for nighttime BP, when ambulatory recordings were repeated in subjects selected for being strong dippers or nondippers on a first registration. Nondippers may also become accustomed to the recorder and sleep more deeply at repeat examinations. Moreover, the night-day ratio incorporates the daytime as well as nighttime pressure, both of which are variable measurements[3] and together contribute to the overall variance of the ratio.

The prognostic significance of the proposed 100% threshold for the night-day ratio also requires further investigation. The ratio is measured on a continuous scale. Dichotomizing continuous measurements introduces potential bias, especially if the dividing line is not determined in advance or is generally agreed on but is determined to fit a given set of data. Further studies on the possible association between dipping status and any outcome variable of interest, regardless of whether the design is cross-sectional or longitudinal, would gain credibility if the findings would be backed up by analyses on a continuous rather than dichotomous scale. Such an approach has the advantage of eliminating the need for arbitrary thresholds and allows visual representation of the association under study over the full range of night-day ratios.

Despite the uniform definitions of night and day in the present study, the nocturnal BP fall tended to be more pronounced in Europeans than Asians. The Asians were 96% Japanese. Their BP had been recorded with gas-powered recorders (Table 1), which operate almost noiselessly[39] and which are therefore assumed to interfere less with sleep quality. These devices[39] provide simultaneous auscultatory and oscillometric readings, but only the latter were analyzed. However, the intercontinental differences in the nocturnal BP fall could not be ascribed to the technique of ambulatory monitoring because they persisted in analyses confined to the oscillometric recordings.

In the present investigation, data handling was rigorously standardized, but data collection was uniform only within each subsample. Thus, selective recruitment, confounding, and methodological differences could have contributed to the apparently lesser nocturnal BP fall in the Japanese. However, recent studies in China[29] and Taiwan[49] showed that nighttime BPs dropped by only 2%,[49] to 11%[29] of the corresponding daytime levels. Normotensive Taiwanese were characterized by low daytime (118/75 mm Hg) and high nighttime (114/71 mm Hg) BPs.[49] Furthermore, in a Japanese population study,[20] in which the daytime pressures averaged 127/75 mm Hg, the day-night differences (15/12 mm Hg) tended to be smaller than in Irish bank employees (18/17 mm Hg)[17] and Belgian citizens (17/15 mm Hg).[26] Thus, a lesser nocturnal BP fall has been observed in three independent studies in the Far East, including one with low[49] and one with high[20] daytime pressures. This suggests that the higher night-day BP ratios in Asian populations could be real and attributable at least in part to genetic background, lifestyle,[47,48,50] or both. The latter hypothesis also mirrors observations in black American adolescents,[51] who, compared with their white counterparts, had a higher nighttime BP, probably as a consequence of environmental rather than genetic determinants.[52]

The nocturnal BP fall and night-day ratios showed a curvilinear correlation with age (Fig 3). These relations were compatible with a smaller nocturnal decrease in BP and higher night-day ratio in older subjects, especially those older than 70 years of age. In the Belgian population,[3] an inverse correlation between the nocturnal fall in diastolic BP and age has already been noticed. The partial regression coefficient, adjusted for sex and body mass index, was compatible with a lesser nocturnal BP fall of 0.7 mm Hg per decade of life. Similar observations for systolic and diastolic BPs have been reported in other European[53-55] and Asian[28,29,56] populations. In general, older people spend more time in bed than younger people, but they experience reduced slow-wave sleep, more nighttime wakefulness, and increased fragmentation of sleep by awake periods.[57] These age-related changes in the circadian sleep-wake rhythm[57] probably explain why the highest night-day BP ratios were observed in older subjects and why there was no dissociation between the age-related patterns in the nocturnal decline of BP and pulse rate.

In the present analysis, the nocturnal BP fall was less pronounced and the night-day ratios were higher when auscultatory rather than oscillometric devices were used. Auscultatory and oscillometric readings have in general the same accuracy vis-à-vis intra-arterial recordings[39,58] or a mercury standard operated by auscultating observers.[39,58] We did not design the present study to identify differences between the two recording techniques, and confounding or aspecific factors could therefore have been involved. However, when people are sleeping in close contact with the bed cover, sound artifacts mimicking the Korotkoff sounds may be generated by involuntary arm movements. Such artifacts may not always be picked up by the algorithms stored in the monitors. Adjusting for body mass index removed the systolic differences between the recording techniques and attenuated the diastolic differences. Thus, in obese arms, the adipose tissue may hamper the propagation of faint Korotkoff sounds from the brachial artery to the microphone, especially at night when BP is lower.

In conclusion, the night-day BP ratio depends less on BP level than on the nocturnal fall in BP and may therefore be preferable for characterizing dippers as opposed to nondippers. The mathematical definition of nondipping, ie, a night-day ratio equal to or higher than unity (100%), corresponds nearly with the 95th percentiles of the ratios in normotensive subjects. The application of this criterion to both systolic and diastolic BPs results in an overall prevalence of nondipping of 3.2%, with a distinct age-related increase. The reproducibility of nondipping and the prognostic significance of the ratio, obviously, need further clarification.

Acknowledgments

Dr Leszek Bieniaszewski was the recipient of a fellowship awarded by the Science Policy Office, Prime Minister's Services, Brussels, Belgium. The expert assistance of Rebecca Crabbé and Sylvia Van Hulle is gratefully acknowledged.

The members of the "Ad Hoc" Working Group were as follows (asterisks mark the names of the Committee Members, whose comments were taken into account and who confirmed their approval of this analysis): Guramy G. Arabidze,* Cardiology Research Center, Moscow, Russian Federation; Neil Atkins,* Eoin T. O'Brien,* The Blood Pressure Unit, Beaumont Hospital, Dublin, Ireland; Peter Baumgart, Medizinische Poliklinik, Westfälische Wilhelms-Universität, Münster, Germany; Leszek Bieniaszewski,* Department of Hypertension and Diabetology, Medical Academy of Gdansk (Poland); Paul De Cort,* Frank Buntinx,* Jan Heyrman,* Academisch Centrum voor Huisartsgeneeskunde, Katholieke Universiteit Leuven (Belgium); Jean-Paul Degaute,* Hôpital Erasme, Université Libre de Bruxelles (Belgium); Primoz Dolenc,* Jurij Dobovisek,* Department of Internal Medicine, Bolcina "Dr Petra Drzaja," Ljubljana, Slovenia; Régis De Gaudemaris,* Centre Hospitalier Régional et Universitaire de Grenoble (France); Inger Enström,* Vårdcentralen, Kävlinge, Sweden; Giuliana Ginocchio,* Franco Macor,* Paolo Palatini,* Istituto di Medicina Clinica, Università di Padova (Italy); Philippe Gosse,* Centre Hospitalier Régional de Bordeaux (France); Steve Gourlay,* Barry P. McGrath, Department of Social and Preventive Medicine, Monash Medical School, Melbourne, Australia; Hilde Celis,* Robert Fagard,* Jan A. Staessen,* Lutgarde Thijs,* Hypertensie en Cardiovasculaire Revalidatie Eenheid, Departement voor Cardiovasculair en Moleculair Ondenzoek, Katholieke Universiteit Leuven (Belgium); Hiroshi Hayashi,* The First Department of Internal Medicine, Nagoya University (Japan); Yutaka Imai,* The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan; Gary James,* Thomas G. Pickering, Cardiovascular Center, The New York (NY) Hospital Cornell Medical Center; Terukazu Kawasaki,* Institute of Health Science, Kyushu University, Kasuga, Japan; Emilio Kuschnir,* Division of Clinical Research, Universidad Nacional de Córdoba (Argentina); Iwao Kuwajima,* Tokyo (Japan) Metropolitan Geriatric Hospital; Lars Lindholm,* Health Sciences Centre, Lund University, Dalby, Sweden; Lisheng Liu,* Jian Ming,* Jiguang Wang,* Fu Wai Hospital and Cardiovascular Institute, Beijing, People's Republic of China; Giuseppe Mancia, Stefano Omboni, Gianfranco Parati,* Istituto di Clinica Medica Generale e Terapia Medica, Università degli Studi di Milano (Italy); Martin Middeke,* Medizinische Poliklinik, Ludwig-Maximilians-Universität München (Germany); Kuniaki Otsuka,* Daini Hospital Department of Medicine, Tokyo (Japan) Women's Medical College; Carl Pieper, Center for the Study of Aging and Human Development, Duke University Medical Center, Durham, NC; Paolo Verdecchia,* Ospedale R. Silvestrini, Unità Organica di Malattie Cardiovasculari e Medicina Interna, Perugia, Italy; Prince K. Zachariah, Mayo Clinic Jacksonville (Fla); Weizhong Zhang,* Shanghai Institute of Hypertension, Shanghai, People's Republic of China.

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