Original Research

Nocturnal Hypertension: Poor Correlation with Office Blood Pressure but Strong Prognostic Factor for Target Organ Damage

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Introduction: We investigated the correlation between systolic and diastolic nocturnal blood pressure (BP) values and office BP values, as well as parameters of 24-hour ambulatory BP monitoring, in patients with hypertension. In addition, we compared nocturnal hypertensives with nocturnal normotensives regarding their demographic, clinical, and laboratory characteristics, as well as other data from 24-hour BP monitoring.

Methods: The study included 182 consecutive patients who had newly diagnosed, never treated, uncomplicated arterial hypertension. Blood samples were obtained from all patients for the determination of glycaemic and lipidaemic profiles. All underwent a complete echocardiographic examination, including tissue Doppler imaging, measurement of carotid intima–media thickness, measurement of carotid–femoral pulse wave velocity, and determination of the augmentation index of reflected waves (Aix@75), as well as 24-hour ambulatory BP monitoring. The population was divided into nocturnal normotensives (NN, n=77) and nocturnal hypertensives (NH, n=105, nocturnal BP >120/70 mmHg).

Results: Although the NH did not differ from the NN as regards the classical cardiovascular risk factors, they showed an excessive inotropic response to exercise (61.9% vs. 22.7%, p=0.028), higher levels of serum uric acid (5.5 ± 1.56 mg/dl vs. 4.7 ± 1.36 mg/dl, p=0.003), as well as greater arterial stiffness, as expressed by a higher carotid–femoral pulse wave velocity (8.6 ± 1.6 m/s vs. 7.9 ± 1.4 m/s, p=0.009), and a greater carotid intima–media thickness (0.74 ± 0.17 mm vs. 0.68 ± 0.15 mm, p=0.007). In addition, although the two groups did not differ significantly as regards office BP values and did not show strong correlations between nocturnal and office BP, both nocturnal diastolic and, especially, systolic BP showed strong correlations with levels of serum uric acid and with subclinical lesions in the heart, central aorta, peripheral vessels, and renal vasculature.

Conclusions: Nocturnal BP is poorly correlated with office BP values. However, the presence of nocturnal hypertension is associated with morphological and functional disturbances of the cardiovascular net. 24-hour ambulatory BP monitoring is an essential tool for revealing this subgroup of hypertensive patients who are at increased cardiovascular risk.

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Many investigators consider the blood pressure (BP) during nocturnal sleep to be the representative value for the organism, given that it is not affected by psychological,[1] dietary, or other habits that affect daytime behaviour.[2] In addition, an inadequate drop in BP during nocturnal sleep (non-dipping status), which has been studied extensively and has been correlated with target organ damage and a bad prognosis, is not an identical concept to that of nocturnal hypertension. The international literature does not report any correlation

between nocturnal BP and office BP, while the relation between the presence of nocturnal hypertension and target organ damage, in contrast to the dipping state, remains controversial.[3-6]

The aim of the present study was to investigate the correlation between nocturnal systolic and diastolic BP values and the corresponding office values, as well as parameters from 24-hour BP monitoring. We also compared nocturnal hypertensives with nocturnal normotensives regarding their demographic, clinical, and laboratory characteristics, as well as other data from 24-hour BP monitoring.

Methods

Study population

This was a cross-sectional study that included 182 consecutive patients who had newly diagnosed, never treated, uncomplicated arterial hypertension, stage I-II. The diagnosis and stratification of the hypertension were based on recent guidelines[7] for the treatment and management of hypertension (office BP ≥140/90 mmHg, confirmed by 24-hour BP monitoring ≥130/80 mmHg). Secondary hypertension was ruled out using the procedure suggested in the international literature.[8,9]

Patients with a history or a clinical indication of coronary artery disease, congestive heart failure, valvular disease, chronic obstructive pulmonary disease, a permanent pacemaker, or atrial fibrillation, were excluded from the study, as were those patients with morbid obesity (body mass index >40 kg/m^2), and those with a significant chronic systemic disease, including diabetes mellitus and chronic renal failure. In order to ensure the evaluation of nocturnal blood pressure would be as accurate as possible, night workers were not included in the study. In addition, subjects with <80% valid daytime or night-time measurements on each ambulatory blood pressure recording (n=17), and those who reported significantly disturbed sleep (n=14) because of the examination were also excluded from the study. Subjects with isolated white-coat hypertension were also excluded, given that this population shows intermediate characteristics compared with normotensive individuals and hypertensive patients.

Methodology

The study protocol was approved by our hospital's ethics committee and conformed to the 1964 Declaration of Helsinki. All subjects gave their written informed consent.

BP measurements and definitions

Office blood pressure was measured on three separate visits, at least one week apart, in accordance with the recent guidelines of the European Society of Hypertension.[7] On each visit, three BP measurements were made at two-minute intervals, after the subject had refrained from coffee, exercise, and smoking for at least 30 min, and had relaxed for at least 5 min sitting in a quiet environment. The mean value of the last two measurements on each visit was determined, and the mean value of the three visits was taken as the office BP. The 24-hour ambulatory BP monitoring was performed during the working day, using SpaceLabs 90207 units (Redmond WA, USA). Briefly, the pressure meter was placed on the non-dominant upper limb, and measurements were made every 15 min during the day and every 20 min during the night. The daytime and night-time periods were determined using a special questionnaire that the patients completed, which included questions about the times they went to bed and got up, as well as questions about the quality of sleep and physical activity during the recording period. Based on the nocturnal BP levels (systolic BP >120 mmHg and/or diastolic BP >70 mmHg) the study population was divided into two groups: nocturnal hypertensives (NH, n=105) and nocturnal normotensives (NN, n=77).

All participants underwent a full clinical examination and an evaluation of their metabolic profile, including high-sensitivity C-reactive protein (hs-CRP), 12-lead ECG, a full echocardiographic examination, determination of carotid–femoral pulse wave velocity (PWV), using a Complior SP device, and the augmentation index (Aix@75), using a Sphygmocor device, as well as echocardiographic determination of the intima–media thickness of the posterior wall of the common carotid arteries 1 cm before the origin of the carotid bulb. In addition, the patients underwent a maximal treadmill exercise test using the Bruce protocol,[10,11] as well as determination of flow-mediated dilation in the brachial artery following 4 minutes' ischaemic ligation, in accordance with international guidelines.[12]

Laboratory tests

Venous blood samples were taken between 8 am and 9 am, after overnight fasting, for the evaluation of gly-

caemic and lipidaemic profiles, uric acid levels, creatinine and electrolytes, as well as indexes of thrombosis (fibrinogen, homocysteine, lipoprotein Lp(a)), inflammation (hs-CRP) and neurohormonal activation (brain natriuretic peptide, BNP).

Estimated glomerular filtration rate (eGFR) was calculated according to the modification of diet in renal disease (MDRD) formula.[13] The levels of hs-CRP were evaluated using a validated high-sensitivity test (Dade Behring CardioPhase hsCRP, Marburg, Germany) with a coefficient of variation of 3.4%.[13] BNP was determined by an immunometric assay using the validated analyser Triage MeterPro (Biosite, Inc.). The BNP levels detected ranged from 5-1300 pg/ml, while the accuracy of the method, the analytical sensitivity, and the stability characteristics have been described in previous studies.[14]

Echocardiography

All participants in the study underwent an echocardiographic examination by an experienced operator, who was unaware of the patients' clinical details or BP data, using a General Electric Vivid 5 echocardiogram device with a 2.5-5 MHz transducer, in accordance with the guidelines of the American Society of Echocardiography.[15] The left atrial diameter was measured from the two-dimensional M-mode recording in the parasternal long-axis view, while the apical four-chamber view was used to determine the cephalocaudal and frontal diameters. These three diameters were used to calculate the left atrial volume, which was normalised to body surface area. The mass of the left ventricle was calculated using the formula of Devereux et al,[16] and was corrected for height because of a mean body mass index above normal levels, which would have underestimated the left ventricular mass index (LVMI).[17] The maximum velocities of the E and A waves of transmitral flow were measured using pulsed Doppler and their ratio, together with the established Doppler indexes of left ventricular diastolic filling (ratio of maximum velocities of the E/A waves of transmitral flow, isovolumic relaxation time, E-wave deceleration time) were evaluated as indexes of diastolic function. Tissue Doppler imaging (TDI) was used to determine the systolic and diastolic tissue velocities of the six basal segments of the left ventricle and the mean of the six values was used to evaluate the systolic (Sm) and diastolic (Em, Am) left ventricular performance.

Statistical analysis

Continuous variables with a normal distribution are given as mean ± standard deviation or, in the case of an asymmetrical distribution, as median and range. Because of its asymmetrical distribution, hs-CRP was transformed logarithmically and the regularity of the transformed variable was verified before the statistical analysis. Categorical variables are given as absolute and relative frequencies. Between-group comparisons were performed using the Student t-test or the chi-square test, as appropriate. Analysis of covariance was used to examine any differences between the groups after adjustment for confounding factors. Correlations between nocturnal systolic and diastolic and office BP values were evaluated using Pearson's correlation coefficient. The statistical analyses were carried out using the SPSS 15.0 software package (SPSS Inc, Chicago, IL, USA). A p-value <0.05 was considered as statistically significant.

Results

The NH patients did not differ significantly from the NN as regards age (Table 1). This hypertensive population was predominantly middle-aged (50.8 ± 12.8 years) and women made up one third of the total. The sex distribution was similar in both the study groups, and two thirds of the women were menopausal.

In addition, the majority of the patients were overweight (52.2%); 21.4% had a normal weight and 26.4% were obese. However, abdominal obesity, as defined in terms of waist circumference (>102 cm for men and >88 cm for women) was present in only 23.1% of the patients. Thus, less than one third of the patients in both groups had the typical characteristics of metabolic syndrome (at least 3 of the 5 items required by Adult Treatment Panel III). Snoring history was evaluated using the validated Epworth clinical questionnaire. Patients with a high score were excluded from the present study and were referred for further investigation in a sleep study. In our study, at least half the patients from each group reported a history of snoring, but with low Epworth grades. Around 40% of the patients in both groups reported a family history of cardiovascular disease.

The active smokers in both groups represented a third of the study population, while former smokers, defined as patients who had not smoked during the previous year, made up 24.7% and non-smokers 41.8%. The mean smoking duration of the smokers

Table 1. Clinical and demographic data of the study population.

	NH	NN	p
Age (years)	51 ± 12	50 ± 13	NS
Sex (% women)	30.5	40.3	NS
Menopause (%)	56.3	61.3	NS
Body mass index (kg/m^2)	28.4 ± 3.8	27.4 ± 3.6	NS
Waist circumference (cm)	94 ± 10	96 ± 11	NS
Waist/hip ratio	0.90 ± 0.07	0.89 ± 0.06	NS
Metabolic syndrome (%)	28.9	29.7	NS
Ten-year cardiovascular risk according to Framingham Score	11.8 (6.6-19.9)	12.8 (7.2-19.7)	NS
Ten-year risk according to HeartScore	1.2 (0.3-4.7)	1.5 (0.4-3.4)	NS
Patients with a moderate added risk according to the ESH (%)	54	52	NS
Patients with a high added risk according to the ESH (%)	42	47	NS
Active smokers (%)	34.3	32.5	NS
Years of smoking	21 ± 12	22 ± 10	NS
Number of cigarettes: <10, 10-20, >20 daily (% patients)	10-11-27	12-13-25	NS
Family history of cardiovascular disease (%)	42.2	39.5	NS
Snoring (%)	55.4	57.3	NS
Excessive inotropic response during exercise (%)	61.9	22.7	0.028

NH – nocturnal hypertensives; NN – nocturnal normotensives; ESH – European Society of Hypertension.

exceeded 20 years in both groups and did not differ significantly. In addition, the percentages of patients who smoked <10, 10-20 and >20 cigarettes per day were similar in the two groups (NH: 10%, 11% and 27%. NN: 12%, 13% and 25%, respectively).

In the whole population the 10-year risk of cardiovascular morbidity and mortality according to the Framingham score was 12.65% (interquartile range 6.8-19.7%) and there was no significant difference between the two study groups. A plurality of the patients (41%) had a risk of <10%, while risk levels of 10-15%, 15-20%, 20-30%, and >30% were found in 17.1%, 18.1%, 11.4%, and 12.4% of patients, respectively.

Similarly, in the overall population the 10-year risk of cardiovascular mortality according to the HeartScore[18] was 1.36% (0.37-4.2%) and did not differ significantly between the two study groups. About half the patients (46.8%) had a 10 year risk <1%, while a low risk (1-2%), moderate risk (2-5%), high risk (5-10%), and very high risk (>10%) were found in 12.3%, 21.4%, 13%, and 6.5% of the patients, respectively.

Categorising the patients based on the risk classification proposed by the European Society of Hypertension revealed that the majority (53.3%) showed a moderate added risk, while 44% had a high added risk, with only 2.7% of patients having a small added risk. No patient had a very high added risk, given that diabetic patients and those with established cardiovascular, cerebrovascular, or renal disease had been excluded from the study.

One interesting observation is that, even though the two groups of hypertensive patients did not differ in any of the above demographic and clinical characteristics, the majority of the NH patients (61.9%) showed an excessive inotropic response during maximal treadmill stress testing, while this was seen in only 22.7% of the NN patients.

The NH patients had significantly lower blood glucose levels than the NN (95 ± 12 versus 99 ± 10, p=0.017), even though they did not differ significantly as regards levels of glycosylated haemoglobin (5.4 ± 0.42 versus 5.5 ± 0.37; Table 2). The NH patients also had significantly higher uric acid levels compared with the NN hypertensives (5.5 ± 1.56 versus 4.7 ± 1.36, p=0.003).

The patients in this study, who had new, uncomplicated hypertension, had normal kidney function, as indicated by serum creatinine levels (0.9 ± 0.18 in both groups) and by the MDRD measure of creatinine clearance (86 ± 19 versus 81 ± 17, p: NS). Ninety-seven percent of the patients had a GFR MDRD >60 mL/min/1.73 m^2 and only 3% (all women) had values between 30-60 mL/min/1.73 m^2.

In addition, the albumin–creatinine ratio in morning urine samples was within the normal range for the overall population (7 mg/g, IR: 5-11 mg/g) and did not differ significantly between the two groups (NH: 8.5 mg/g, 5.2-11.7, and NN: 6 mg/g, 5-9.5).

The two groups of patients also showed no statistically significant differences as regards lipidaemic profile and indexes of thrombosis (fibrinogen, homo-

Table 2. Comparison of the biochemical data in the study population.

	NH	NN	p
Blood glucose	95 ± 12	99 ± 10	0.017
HbA1c	5.4 ± 0.42	5.5 ± 0.37	NS
Creatinine	0.9 ± 0.18	0.9 ± 0.18	NS
GFR MDRD	86 ± 19	81 ± 17	NS
Uric acid	5.5 ± 1.56	4.7 ± 1.36	0.003
Log hs-CRP	0.018 ± 0.46	-0.027 ± 0.61	NS
Total cholesterol	212 ± 38	219 ± 35	NS
Triglycerides	124 ± 62	116 ± 55	NS
HDL-cholesterol	50 ± 14	52 ± 11	NS
Log Lp(a)	1.1 ± 0.4	1 ± 0.5	NS
Log homocysteine	1 ± 0.19	1 ± 0.15	NS
Fibrinogen	337 ± 66	351 ± 82	NS
Log BNP	1 ± 0.37	1 ± 0.39	NS
Log ACR	0.99 ± 0.37	0.89 ± 0.34	NS

NH – nocturnal hypertensives; NN – nocturnal normotensives; HbA1c – glycosylated haemoglobin; GFR – glomerular filtration rate; MDRD – modification of diet in renal disease; hs-CRP – high sensitivity C-reactive protein; BNP – brain natriuretic peptide; ACR – albumin–creatinine ratio.

cysteine, Lp(a)), inflammation (hs-CRP), and neurohormonal activation (BNP).

The NH group did not differ significantly from the NN patients regarding any of the indexes of early damage to the left ventricle or the left atrium, although the indexes were all arithmetically more affected in the NH group, with the sole exception of left ventricular mass index normalised to height$^{2.7}$ (Table 3). In addition, the augmentation index of reflected waves (Aix@75) and the flow mediated dilation in the brachial artery did not differ significantly between the NH and NN groups (26 ± 99 versus 25 ± 10, and 5.4 ± 3.6 versus 6 ± 4.1%, respectively).

In contrast, the NH group showed significantly greater intima–media thickness of the posterior wall of the common carotid arteries (0.74 ± 00.17 versus 0.67 ± 0.15, p=0.007) and greater carotid–femoral PWV (8.5 ± 1.6 versus 7.9 ± 1.4, p=0.009), two validated indexes of arterial stiffness.

Although the two groups of hypertensive patients did not differ significantly as regards the office systolic, diastolic and mean BP, pulse pressure, or office heart rate, on 24-hour ambulatory BP monitoring the NH group showed significantly greater values for the whole 24 hours, for daytime and night-time separately, diastolic and mean BP (p<0.001 for all), as well as for nocturnal pulse pressure (Table 4). The heart rate did not differ significantly between the groups in any of the measurements (office, 24-hour, day, night). In contrast, the NH group showed a significantly lower

Table 3. Comparison of target organ damage in the study population.

	NH	NN	p
Transmitral E/A ratio	1 ± 0.33	1.1 ± 0.31	NS
DecT	207 ± 53	201 ± 42	NS
IVRT	100 ± 22	96 ± 18	NS
TDI Em/Am	0.95 ± 0.4	0.94 ± 0.26	NS
LAVI	22 ± 5	20 ± 5	NS
LVMI	38 ± 7.7	39 ± 9.2	NS
FMD brachial artery (%)	5.4 ± 3.6	6 ± 4.1	NS
Aix@75 (%)	26 ± 9	25 ± 10	NS
Carotid–femoral PWV (m/s)	8.6 ± 1.6	7.9 ± 1.4	0.009
Carotid IMT (mm)	0.74 ± 0.17	0.68 ± 0.15	0.007

NH – nocturnal hypertensives; NN – nocturnal normotensives; DecT – deceleration time; IVRT – isovolumic relaxation time; TDI – tissue Doppler imaging; LAVI – left atrial volume index; LVMI – left ventricular mass index; FMD – flow-mediated dilation; Aix@75 – augmentation index of reflected waves; PWV – pulse wave velocity; IMT –intima–media thickness.

Table 4. Blood pressure (BP) and heart rate data.

	NH	NN	p
Systolic office BP (mmHg)	147 ± 14	144 ± 13	NS
Diastolic office BP (mmHg)	93 ± 8	92 ± 9	NS
Mean office BP (mmHg)	111.6 ± 9	109.5 ± 8.6	NS
Office pulse pressure (mmHg)	54 ± 12	52 ± 12	NS
Office heart rate (bpm)	71 ± 11	70.7 ± 12	NS
24-hour systolic BP (mmHg)	130 ± 9	122 ± 9	<0.001
24-hour diastolic BP (mmHg)	79.5 ± 10.5	73.5 ± 7.6	<0.001
24-hour mean BP (mmHg)	96 ± 8.5	89.8 ± 7.3	<0.001
24-hour pulse pressure (mmHg)	50.5 ± 11.3	48.6 ± 7.1	NS
24-hour heart rate (bpm)	73.5 ± 8.8	73.9 ± 8.2	NS
Daytime systolic BP (mmHg)	133.8 ± 12.8	126.3 ± 10	<0.001
Daytime diastolic BP (mmHg)	82.5 ± 9	76.7 ± 8.5	<0.001
Daytime mean BP (mmHg)	99 ± 8.4	93 ± 8.3	<0.001
Daytime pulse pressure (mmHg)	51 ± 11.7	49.6 ± 7.5	NS
Daytime heart rate (bpm)	76 ± 9	76 ± 8.5	NS
Night-time systolic BP (mmHg)	123 ± 9.4	108 ± 7	<0.001
Night-time diastolic BP (mmHg)	73.6 ± 7.1	62 ± 5.3	<0.001
Night-time mean BP (mmHg)	90.6 ± 7.7	77.6 ± 5	<0.001
Night-time pulse pressure (mmHg)	49.6 ± 9.8	45.6 ± 6.8	0.002
Night-time heart rate (bpm)	65.6 ± 8.8	63.7 ± 7.3	NS
Night-time drop in systolic BP (%)	7.4 ± 7.8	14.2 ± 6.2	<0.001
Night-time drop in diastolic BP (%)	10.2 ± 8.6	18.2 ± 7.2	<0.001
Night-time drop in mean BP (%)	8.3 ± 8	16.4 ± 6.5	<0.001
Night-time drop in pulse pressure (%)	2 ± 12	7.5 ± 8.5	0.001
Night-time drop in heart rate (%)	13.8 ± 8.2	17 ± 6.7	0.006

nocturnal drop in systolic (7.4 ± 7.8% versus 14.2 ± 6.2%, p<0.001), diastolic (10.2 ± 8.6% versus 18.2 ± 7.2%, p<0.001), mean (8.3 ± 8% versus 16.4 ± 6.5%, p<0.001), and pulse pressure (2 ± 12% versus 7.5 ± 8.5%, p=0.001) than the NN group, as well as a lower heart rate (13.8 ± 8.2% versus 17 ± 6.7%, p=0.006).

Nocturnal systolic BP was not correlated with diastolic office BP, and nocturnal diastolic BP was not correlated with systolic office BP (Table 5). In contrast, nocturnal systolic BP showed strong positive correlations with systolic and mean office BP, and office pulse pressure. Similarly, nocturnal diastolic BP had a strong positive correlation with diastolic and mean office BP, and a strong negative correlation with office pulse pressure (r=-0.186, p=0.012).

In addition, nocturnal systolic BP had strong positive correlations with 24-hour systolic, diastolic, and mean BP, as well as with daytime systolic, diastolic and mean BP, and pulse pressure. In contrast, nighttime diastolic BP showed strong positive correlations with 24-hour systolic, diastolic, and mean BP, as well as with daytime systolic, diastolic, and mean BP, but had a negative correlation with 24-hour and daytime pulse pressure.

Both systolic and diastolic nocturnal BP had a strong negative correlation with the nocturnal drop in systolic BP and with the nocturnal drop in diastolic and mean BP. In contrast, only nocturnal systolic BP had a strong negative correlation with the nocturnal drop in pulse pressure (r=-0.378, p<0.001) and the heart rate (r=-0.341, p<0.001).

Finally, especially systolic, but also diastolic nocturnal BP had a strong positive correlation with the response to exercise of both systolic and diastolic BP.

Entire population (Table 6)

Nocturnal systolic BP had a strong positive correlation with height (r=0.161, p=0.030), body surface area (r=0.163, p=0.028), uric acid (r=0.282, p=0.01), carotid–femoral PWV (r=0.243, p=0.001), left atrial volume index (r=0.243, p=0.01), and carotid artery intima–media thickness (r=0.234, p=0.002). Nocturnal diastolic BP had a strong positive correlation with height (r=0.159, p=0.032), and smoking (r=0.168, p=0.011), but a negative correlation with age (r=0.258, p<0.001), and with the peak velocity of the mitral A-wave (r=-0.200, p=0.007).

Table 5. Correlations between nocturnal blood pressure (BP), office BP and other data from 24-hour monitoring, as well as the inotropic response of BP during exercise.

	Nocturnal systolic BP	Nocturnal diastolic BP
Systolic office BP	r=0.291, p<0.001	NS
Diastolic office BP	NS	r=0.248, p=0.001
Mean office BP	r=0.157, p<0.034	r=0.147, p=0.047
Pulse pressure	r=0.335, p<0.001	r=-0.186, p=0.012
24-hour systolic BP	r=0.741, p<0.001	r=0.439, p<0.001
24-hour diastolic BP	r=0.365, p<0.001	r=0.764, p<0.001
24-hour mean BP	r=0.523, p<0.001	r=0.647, p<0.001
24-hour pulse pressure	r=0.514, p<0.001	r=-0.250, p=0.001
Daytime systolic BP	r=0.589, p<0.001	r=0.369, p<0.001
Daytime diastolic BP	r=0.265, p<0.001	r=0.650, p<0.001
Daytime mean BP	r=0.418, p<0.001	r=0.597, p<0.001
Daytime pulse pressure	r=0.452, p<0.001	r=-0.240.p=0.001
Night-time drop in systolic BP	r=-0.583, p<0.001	r=-0.379, p<0.001
Night-time drop in diastolic BP	r=-0.472, p<0.001	r=-0.466, p<0.001
Night-time drop in mean BP	r=-0.561, p<0.001	r=-0.415, p<0.001
Night-time drop in pulse pressure	r=-0.419, p<0.001	NS
Night-time drop in heart rate	r=-0.341, p<0.001	NS
Maximum SBP during exercise	r=0.490, p<0.001	r=0.323, p=0.027
Maximum DBP during exercise	r=0.444, p=0.002	r=0.321, p=0.028

SBP – systolic blood pressure; DBP – diastolic blood pressure.

Table 6. Correlations between nocturnal blood pressure (BP) and demographic, biochemical, echocardiographic, and angiological data for the entire patient population.

	Nocturnal systolic BP	Nocturnal diastolic BP
Age	NS	r=-0.258, p<0.001
Height	r=0.161, p=0.030	r=0.159, p=0.032
BSA	r=0.163, p=0.028	NS
Smoking	NS	r=0.168, p=0.046
Haemoglobin	NS	r=0.239, p=0.018
Uric acid	r=0.282, p=0.01	r=0.210, p=0.011
Log PWV	r=0.243, p=0.001	NS
LAVI	r=0.297, p<0.001	NS
Peak mitral A-wave velocity	NS	r=-0.200, p=0.007
Carotid IMT	r=0.234, p=0.002	NS

BSA – body surface area; PWV – pulse wave velocity; LAVI – left atrial volume index; IMT – intima–media thickness.

Women (Table 7)

Nocturnal systolic BP had a strong positive correlation with salt consumption (r=0.272, p=0.031), uric acid (r=0.295, p=0.029), PWV (r=0.310, p=0.015), peak velocity of the mitral A-wave (r=0.287, p=0.029), the E/Em ratio (r=0.448, p=0.001), and carotid artery intima–media thickness (r=0.326, p=0.013), while having a strong negative correlation with exercise levels (r=-0.253, p=0.046), peak tissue E-wave velocity (r=-0.317, p=0.011), and the tissue Em/Am ratio (r=-0.319, p=0.011). In contrast, nocturnal diastolic BP only had a negative correlation with age (r=-0.289, p=0.021).

Men (Table 8)

Nocturnal systolic BP had a strong positive correlation with uric acid levels (r=0.223, p=0.34), the albumin–creatinine ratio (r=0.364, p=0.032), PWV (r=0.224, p=0.016), left atrial volume index (r=0.294, p=0.001), and carotid artery intima–media thickness (r=0.202, p=0.035). In contrast, nocturnal diastolic BP had a strong negative correlation with age (r=-0.199, p=0.030), blood glucose levels (r=-0.236, p=0.018), and peak mitral A-wave velocity (r=-0.243, p=0.013), having a strong positive correlation only with MDRD creatinine clearance (r=0.203, p=0.042).

Table 7. Correlations between nocturnal BP and demographic, biochemical, echocardiographic, and angiological data for women.

	Nocturnal systolic BP	Nocturnal diastolic BP
Age	NS	r=-0.289, p=0.021
Salt consumption	r=0.272, p=0.031	NS
Exercise	r=-0.253, p=0.046	NS
Uric acid	r=0.295, p=0.029	NS
PWV	r=0.310, p=0.015	NS
Peak mitral A-wave velocity	r=0.287, p=0.029	NS
TDI E peak velocity	r=-0.317, p=0.011	NS
TDI E/Em	r=0.448, p=0.001	NS
TDI Em/Am	r=-0.319, p=0.011	NS
Carotid IMT	r=0.326, p=0.013	NS

Abbreviations as in previous tables.

Table 8. Correlations between nocturnal BP and demographic, biochemical, echocardiographic, and angiological data for men.

	Nocturnal systolic BP	Nocturnal diastolic BP
Age	NS	r=-0.199, p=0.030
Blood glucose	NS	r=-0.236, p=0.018
GFR MDRD	NS	r=0.203, p=0.042
Uric acid	r=0.223, p=0.034	NS
Log ACR	r=0.364, p=0.032	NS
Log PWV	r=0.224, p=0.016	NS
LAVI	r=0.294, p=0.001	NS
Mean mitral A-wave velocity	NS	r=-0.243, p=0.013
Log carotid IMT	r=0.202, p=0.035	NS

Abbreviations as in previous tables.

Discussion

In the total population the nocturnal systolic and diastolic BP were not correlated with the diastolic and systolic office BP, respectively, but only with the mean BP and pulse pressure, and with the 24-hour and daytime systolic, diastolic and mean BP, and pulse pressure. This finding, taken together with the fact that, although the two groups of hypertensive patients did not differ as regards their office BP levels, the NH patients showed significant differences with respect to the systolic, diastolic, and mean BP, both during the 24-hour monitoring and during the daytime and night-time hours, underlines the need for a more integrated evaluation of BP over a 24-hour period using ambulatory recording devices. The discovery of an inadequate drop in BP during nocturnal sleep (non-dipping) automatically increases the patient's risk and, apart from a thorough investigation of possible secondary causes of hypertension (e.g. sleep apnoea), it is likely to necessitate a modification of the timing of the patient's antihypertensive medication. A number of studies have concluded that 24-hour BP monitoring is a more dependable index of morbidity and mortality than are office BP measurements,[19] and that 24-hour ambulatory BP monitoring is a powerful prognostic index of cardiovascular mortality, independently of office BP or other prognostic indexes.[20]

Apart from their constantly elevated BP values, the NH patients also exhibited a smaller drop in systolic, diastolic and mean BP, and pulse pressure during nocturnal sleep. The same patients also had a significantly smaller drop in heart rate during nocturnal sleep, a finding that probably indicates dysfunction of the autonomic nervous system. The non-dipping of heart rate during nocturnal sleep has been associated with a 2.5-fold increase in the risk of future cardiovascular events, independently of the non-dipping of nocturnal BP and the 24-hour BP levels.[21] A multitude of mechanisms have been implicated for a better explanation of the high nocturnal BP values and the worse outcome of these patients; these include autonomic nervous system dysfunction, baroreceptor disturbances, sleep apnoea, nocturnal fluid retention, and reduced sodium excretion.[22]

Also interesting were the strong correlations—in the

total population, as well as in men and women separately—between nocturnal systolic blood pressure and levels of serum uric acid, carotid–femoral PWV, carotid artery intima–media thickness, and left atrial volume index.

Ample epidemiological and experimental data have led to the conclusion that increased levels of serum uric acid are a significant and independent risk factor for cardiovascular and kidney disease, especially in patients with hypertension, diabetes mellitus, or heart failure. In particular, they are highly prognostic for mortality in patients with heart failure or coronary artery disease, and for cardiovascular events in patients with diabetes mellitus. In addition, patients with hypertension and hyperuricaemia show a 3- to 5-fold risk of developing coronary artery disease or stroke compared to patients with normal uric acid levels. Although the mechanisms by which uric acid promotes cardiovascular disease are unknown, hyperuricaemia is associated with damaging effects on endothelial function, on the metabolism of reactive oxygen species, and on platelet adhesion and coagulation mechanisms. Recent studies have found a correlation between increased levels of uric acid and a non-dip in BP during sleep,[23,24] a finding compatible with the results of our study. In addition, in patients with sleep apnoea the secretion of uric acid and the nocturnal change in the ratio of serum uric acid to creatinine are good indexes for evaluating the effectiveness of the use of continuous positive airway pressure.[25]

Arterial stiffness, expressed either as an increase in carotid–femoral pulse wave velocity or as carotid artery intima–media thickening, is a common pathological finding in patients who have no dip in nocturnal BP,[26,27] so combinations of the previous mechanisms are highly likely to promote vascular dysfunction and to increase arterial stiffness,[28] with the suspicion that hyperuricaemia could play an important role via the mechanisms referred to above.

Furthermore, nocturnal systolic and diastolic BP are strongly and positively correlated with peak systolic BP during exercise. The excessive inotropic response during exercise shown by the NH patients is an indication of pathological control mechanisms (autonomic nervous system, renin–angiotensin–aldosterone system), which maintain BP at steadily high levels throughout the entire 24 hours, without being affected by physiological circadian variations, and in addition are unable to modulate peripheral vascular resistances during exercise.[21] Indeed, in our study more than 60% of the NH patients showed an excessive inotropic response during treadmill exercise testing.

The effect of systemic hypertension on left atrial dilation has been studied extensively. The correlation between high systolic BP or pulse pressure BP and an increase in left atrial dimensions has been described in many studies, including the Framingham study.[29] In the present study, the mean nocturnal systolic BP, but not the mean daytime systolic BP, was strongly correlated with the left atrial volume index. One pathological mechanism that could be implicated is the continuously increased pressure load throughout the entire day, and not only during the night, which is an independent prognostic factor for left atrial dilation.

A significant new finding of this study is that, in men, nocturnal systolic BP, apart from the above-mentioned correlations, also had a strong positive correlation with the albumin–creatinine ratio, an index of early kidney damage in the setting of hypertension which, in combination with hyperuricaemia, causes a worsening of the renal damage. In a large study of hypertensive, non-diabetic patients, it was found that levels of the albumin–creatinine ratio were significantly higher in non-dippers and especially in those who showed nocturnal systolic hypertension. In women, in contrast, nocturnal diastolic BP has a strong negative correlation with age, while nocturnal systolic BP has a strong positive correlation with salt consumption, peak mitral A-wave velocity, and the echocardiographic E/Em ratio, and a strong negative correlation with exercise levels, peak tissue Em-wave velocity, and the ratio of tissue Em/Am velocities from the six basal segments of the left ventricle, all indexes of early left ventricular diastolic dysfunction. These findings are compatible with those of a study by Staessen et al,[30] who observed that women who do not have a dip in BP during the night have an up to 10-fold worse prognosis as regards the occurrence of cardiovascular events, compared to normotensive and hypertensive women with white-coat syndrome.

Conclusions

The main findings of this study are that patients with nocturnal hypertension are characterised by an excessive inotropic response during exercise, increased arterial stiffness, and increased serum uric acid levels. These findings support the hypothesis that a reduced nocturnal dip in BP has an undesirable effect on the cardiovascular system and in addition can be a significant diagnostic criterion for the therapeutic management of these patients. These results are confirmed by the strong correlations between nocturnal diastolic

and, especially, systolic BP, and subclinical damage in the heart, central aorta, peripheral vessels, and renal parenchyma, in both women and men.

In everyday clinical practice, the measurement of office BP is considered a low reliability examination – in recent years more than ever. However, based on the office BP values we are obliged to take important therapeutic decisions about the patient. The information provided by ambulatory BP monitoring provides us with an integrated picture of both the patient's real haemodynamic load and the risk of target organ damage from the hypertension.

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