ORIGINAL ARTICLE

Does sympathetic overactivation feature all hypertensives? Differences of sympathovagal balance according to night/day blood pressure ratio in patients with essential hypertension

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When evaluating the 'night/day BP ratio', both hypertensives and normotensives can be arbitrarily classified into four groups: extreme dippers (ratio ⩽ 0.8), dippers (0.8 < ratio ⩽ 0.9), mild dippers (0.9 < ratio ⩽ 1.0) and reverse dippers (ratio ⩾ 1.0). Reverse and mild dipper hypertensives have poorer prognoses compared with the physiological dipper profile, but the prognostic relevance of the extreme dipper profile remains uncertain. The evaluation of heart rate variability (HRV), obtained by 24-h Holter ECG monitoring, is the most frequently used noninvasive form of assessment of the activity of the autonomic nervous system. Reverse and mild dipper hypertensives have reduced HRV, indicating an overactivation of the sympathetic nervous system (SNS); however, the HRV behavior in extreme dippers is still controversial. The goal of this study was to compare HRV indexes of extreme vs. reverse dipper essential hypertensives measured on the basis of time domains. We enrolled 125 hypertensive subjects, divided in 4 quartiles according to day/night blood pressure (BP) ratios. The upper and lower quartiles (31 subjects per quartile) were compared; 30 normotensive subjects were enrolled as a control group. Time domain HRV parameters of the three groups revealed a higher degree of sympathetic activation in the lower quartile (reverse dipper) vs. the upper quartile (extreme) and normotensive controls. HRV parameters related to parasympathetic tone did not show any significant variations among the three groups. Contrary to common belief, not all hypertensives have SNS overactivation.

INTRODUCTION

The physiological circadian rhythm of blood pressure (BP) includes a nocturnal decrease, described as the 'dipping status', that indicates the behavior of the BP in the transition from wakefulness to sleep. The BP may fall, rise or remain constant, and it is mainly quantified through the so-called 'night/day BP ratio'. On the basis of this index, patients can be arbitrarily classified into four groups: extreme dippers (ratio ⩽ 0.8), dippers (0.8 < ratio ⩽ 0.9), nondippers or mild dippers (0.9 < ratio ⩽ 1.0) and reverse dippers or risers (ratio ⩾ 1.0 indicating a nocturnal increase of BP when compared with the daytime mean values).[1] As noted by the most recent guidelines,[2] these categories are the result of mathematical simplification; therefore, it is not reasonable to expect any clinical and/or prognostic difference between one patient with a nocturnal BP fall of 9.9% and another patient with a nocturnal BP fall of 10.1%, although both patients formally belong to different categories.

Despite this, current knowledge suggests that any variation from the physiological dipper profile is associated with a poorer prognosis.

The nondipper pattern is well recognized as an additive risk factor for cardiovascular events in both hypertensive and normotensive subjects.[3] In addition, it is more frequently associated with end-organ damage, particularly left ventricular hypertrophy[4] and progression to end-stage renal failure,[5] when compared with the dipper pattern. It has been established that reverse dipper hypertensives have the worst prognosis because of the increased incidence of stroke and cardiac events compared with the other profiles,[1,6,7] whereas the prognostic outcome of the extreme dipper profile is much less clear. The extreme dipper category has been associated with higher

relative risk of stroke[7] and silent cerebrovascular damage in elderly hypertensives,[8] but current data regarding increased cardiovascular risk in hypertensives with higher night/day BP ratio are not consistent;[9] therefore, the clinical significance of this phenomenon remains uncertain.

The hypothesis that essential hypertension may include in its multifactorial etiology an abnormal autonomic modulation of BP has been investigated for a long time, both in experimental animals and in humans, and significant results have been obtained. However, it has been more challenging for researchers to find a connection between the circadian fluctuations in the activity of the autonomic nervous system and the BP values in hypertensive subjects. The evaluation of heart rate variability (HRV), obtained by 24-h Holter ECG monitoring, represents the currently most frequently used noninvasive form of assessment of the activity of the autonomic nervous system.[10] A reduced HRV usually indicates an alteration of the sympathovagal balance in favor of the sympathetic nervous system (SNS): this could be the effect of increased sympathetic tone, decreased parasympathetic tone or both.

The assessment of HRV in hypertensives in relation to the circadian rhythm of BP has produced conflicting results. Some observations have reported an inverse association between the degree of sympathetic activation and the extent of the nighttime BP fall in hypertensive subjects,[11–14] whereas others have demonstrated a blunted nocturnal decrease in parasympathetic function (determined by power spectral analysis of HRV) in nondipper hypertensives.[12] Despite the central role that nocturnal sympathetic overactivation appears to play in patients with primary autonomic failure with a reduction in both sympathetic and parasympathetic activities, a high incidence of the nondipping pattern has been observed, thus suggesting that the inability to modulate the sympathovagal balance may be one of the main causes of the blunting of the circadian BP rhythm.[15–18] Only a few studies have attempted to clarify HRV behavior in extreme dipper hypertensives. Kario et al.[19] have reported a higher sympathetic tone in 51 asymptomatic elderly extreme dipper hypertensive patients compared with dippers.

Based on this information, the goal of our study was to compare time domain HRV indexes, indirectly assessed through 24-h Holter ECG monitoring, in a group of essential hypertensives to better clarify the relationship between the activity of the SNS and the sympathovagal balance according to different night/day BP ratios.

METHODS

We enrolled 125 subjects (64 men and 61 women, mean age 63 ± 12.6 years) referred to the UOC of Medicina Interna e Cardioangiologia of the University of Palermo for ambulatory examination during the period between 01 April 2010 and 31 December 2014. All of the subjects enrolled were previously informed about the characteristics and the object of the study, and a written informed consent was required. The main inclusion criterion was essential hypertension, in which hypertension was defined as present if the subjects had been previously diagnosed according to the latest European Society of Cardiology/European Society of Hypertension guidelines and were routinely receiving antihypertensive therapy.[20]

Exclusion criteria were:

- Distance between ambulatory BP monitoring (ABPM) and 24-h Holter ECG monitoring over 30 days;
- Presence of supraventricular arrhythmias (atrial flutter, paroxysmal, persistent or permanent atrial fibrillation);
- Permanent intracardiac pacemakers;
- Evidence of diseases or conditions responsible for secondary hypertension;
- Clinical history or any clinical evidence of sleep apnea syndrome;

- History of depression and/or use or psychotropic drugs;
- History or clinical evidence of orthostatic hypotension, evaluated by comparing sitting and standing BP during the run-in visit;
- Clinical history of autonomic dysfunction or diabetic neuropathy (for diabetic hypertensives);
- Involvement in physical training programs and/or reported regular exercise habit;
- Any conditions compromising the performance and/or the reliability of dynamic ECG and/or ABPM (severe obesity, excessive alcohol consumption, history of sleep disturbance, working night shifts or intolerance to the procedure).

A total of 30 subjects (16 men and 14 women, mean age 43.5 ± 14.7 years) without a history of hypertension and with normal clinical ($<140/90$ mm Hg) and ambulatory (24-h BP $<130/80$, diurnal $<135/85$ and nocturnal $<120/70$) BP values[2] referred to the U.O.C. of Medicina Interna e Cardioangiologia of the University of Palermo for ambulatory examination were enrolled as controls.

The initial study procedure included, for all subjects: a comprehensive medical history with a specific focus on cardiovascular risk profile; pharmacological anamnesis; complete physical examination; assessment of body mass index, calculated as the individual's body weight divided by the square of the patient's height; waist circumference; and blood biochemical examinations (including total cholesterol, high-density lipoprotein cholesterol, triglyceride, creatinine, fibrinogen, complete blood count, fasting glucose and C-reactive protein).

Patients were defined as having type 2 diabetes if they had known diabetes that was being treated by diet, oral hypoglycemic drugs or insulin.

Previous cerebrovascular disease (transient ischemic attack/ischemic stroke) was assessed by history, specific neurological examination performed by specialists and hospital or radiological (brain CT or brain magnetic resonance) records of confirmed previous stroke.

Previous coronary heart disease was detected by history, clinical examination, ECG and echocardiogram. M-mode echocardiography was performed using the General Electric VIVID 7 device (GE HealthCare Ultrasound Cardiology, Horten, Norway) using a 2–4-MHz transducer. Measurement of the cardiac chambers were performed according to the latest recommendations of the American Society of Echocardiography.[21] The left ventricular mass (LV mass) was calculated by using the ASE (Atomistic Simulation Environment) equation: $0.8 \times (1.04 \times ([LVIDD+PWTD+IVSTD]3 - [LVIDD]3)+0.6$ g.[20] The left ventricular hypertrophy was defined as left ventricular mass index (LV mass/Ht$^{2.7}$) $\geqslant 51$ g m$^{-1(2.7)}$ for men and $\geqslant 49.5$ g m$^{-1(2.7)}$ for women.[22] On the basis of history, clinical findings and echocardiographic evaluation, no subjects were affected by congestive heart failure or left ventricular dysfunction.

Subjects were classified as having previous peripheral artery disease when they had a history of ankle-brachial index <0.9 and/or of intermittent claudication, critical limb ischemia or peripheral arterial bypass or amputation.

Diagnosis of liver steatosis was assessed by clinical examination and an abdominal ecography.

Diagnosis of chronic obstructive pulmonary disease (COPD) was assessed by clinical examination and/or clinical records provided by the patients.

ABPM was performed by using the TM–2430 Recorder from the A&D Company (Tokyo, Japan). This device provides an oscillometric record. Our recorders had previously been validated and recommended for clinical use.[2] The monitoring equipment was arbitrarily applied at 0800 h. The cuff was fixed to the nondominant arm, and three BP readings were taken concomitantly with sphygmomanometer measurements to ensure that the average of the two sets of values did not differ by >5 mm Hg. All patients used their prescribed antihypertensive medications during ABPM, without changes in the type of medication, dosage or time of administration throughout the study. The device was set to measure BP at 15 min intervals during the day (0600 to 2200 h) and at 30 min intervals during the night (2200 to 0600 h). During the 24 h of examination, patients were told to keep their arms immobile at the time of the measurements, to keep a diary of daily activities and to return to the hospital 24 h later. The monitoring was always performed on a working day and during normal administration of the usual antihypertensive treatment. The patients had no access to the ambulatory BP values.

Table 1 Demographic and clinic variables—ABPM data— hypertensive subjects vs. controls

Variable	Hypertensives (n 125)	Controls (n 30)	P-value
Number of patients enrolled	125	30	
M/F, n (%)	64/61	16/14	0.21
	(51.2/48.8)	(53.3/46.7)	
Age (years), mean ± s.d.	63 ± 12.65	43.5 ± 14.68	
Duration of hypertension (years), mean ± s.d.	10.9 ± 10.06	—	
Type of hypertension, n (%)			
Target	40 (32.0%)		
Sisto-diastolic	33 (26.4%)	—	
Borderline	5 (4.0%)		
Systolic	47 (37.6%)		
Type of drugs, n (%)			
ACEiS	26 (20.8%)		
ARBs	64 (51.2%)		
Diuretics	33 (26.4%)	—	
CCBs	26 (20.8%)		
β-Blockers	41 (32.8%)		
Other (α-blockers, clonidine)	19 (15.2%)		
Number of drugs, n (%)			
Zero	26 (20.8%)		
One	33 (26.4%)		
Two	30 (24.0%)	—	
Three	29 (23.2%)		
More than three	7 (5.6%)		
Diabetes, n (%)	38 (30.4%)	0	0.001
Fasting glucose (mg dl^{-1}), mean ± s.d.	111.5 ± 38.86	85.6 ± 10.11	0.018
Past cerebral vascular event, n (%)	25 (20.0%)	0	0.001
Past cardiac vascular event, n (%)	25 (20.0%)	0	0.001
Past peripheral arterial disease, n (%)	13 (10.4%)	0	0.001
Creatinin (mg dl^{-1}), mean ± s.d.	0.93 ± 0.3	0.81 ± 0.16	0.013
Creatinine clearance (ml min^{-1}), mean ± s.d.	84.7 ± 32.0	126 ± 34.74	0.002
Statin use, n (%)	68 (54.4%)	1 (3.3%)	0.001
BMI (kg m^{-2}), mean ± s.d.	28.25 ± 4.54	28.2 ± 4.53	0.830
Waist circumference (cm), mean ± s.d.	101.2 ± 11.74	97.9 ± 9.38	0.132
Liver steatosis, n (%)	83 (66.4%)	6 (20.0%)	0.01
COPD, n (%)	11 (8.8%)	0	
Total cholesterol (mg dl^{-1}), mean ± s.d.	185.2 ± 48.84	203.9 ± 33.8	0.182
HDL cholesterol (mg dl^{-1}), mean ± s.d.	49.0 ± 12.06	46.4 ± 8.31	0.128
Triglycerides (mg dl^{-1}), mean ± s.d.	122.3 ± 60.92	122.4 ± 49.46	0.635
Left ventricular hypertrophy, n (%)	19 (15.2%)	0	
Current smokers, n (%)	24 (19.2%)	6 (20.0%)	0.875
Past smokers, n (%)	35 (28.0%)	2 (6.6%)	0.032
24-h SBP (mm Hg)	133.1 ± 12.03	111.8 ± 24.06	0.001
24-h DBP (mm Hg)	75.7 ± 8.52	71.0 ± 4.44	0.069
24-h HR (b.p.m.)	69.3 ± 8.44	75.3 ± 7.28	0.007
Day SBP (mm Hg)	136.6 ± 12.54	122.1 ± 7.75	0.013
Day DBP (mm Hg)	78.3 ± 9.53	74.5 ± 4.89	0.142
Day HR (b.p.m.)	71.6 ± 9.2	79.8 ± 8.31	0.032
Night SBP (mm Hg)	124.7 ± 5.4	105.1 ± 9.82	0.008
Night DBP (mm Hg)	69.6 ± 8.67	63.3 ± 6.53	0.048
Night HR (b.p.m.)	63.9 ± 8.35	65.1 ± 7.24	0.247
Night/day SBP ratio	0.915 ± 0.097	0.859 ± 0.072	0.141
s.d. 24 h SBP (mm Hg)	19.55 ± 4.59	18.04 ± 3.74	0.217
s.d. 24 h DBP (mm Hg)	14.84 ± 4.04	14.43 ± 3.40	0.592

Table 1 (Continued)

Variable	Hypertensives (n 125)	Controls (n 30)	P-value
s.d. 24 h HR (mm Hg)	10.73 ± 6.16	14.82 ± 5.03	0.124
s.d. day SBP (mm Hg)	18.85 ± 5.13	17.42 ± 3.94	0.402
s.d. day DBP (mm Hg)	14.95 ± 4.48	14.68 ± 4.10	0.899
s.d. night SBP (mm Hg)	15.57 ± 11.45	10.84 ± 3.12	0.002
s.d. night DBP (mm Hg)	10.91 ± 6.63	8.58 ± 2.87	0.073

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; M/F, male/female; PAD, peripheral artery disease; SBP, systolic blood pressure.
Creatinine clearance has been calculated through Cockroft and Gault formula.
Data are presented as mean value ± s.d.

Measurements recorded during the 24-h period were stored on a personal computer and screened as follows: a 24-h record was rejected for analysis if more than one-third of the potential day and night measurements were absent or invalid. The ambulatory BP values used for statistical analysis were expressed as 24-h average systolic BP (SBP) and diastolic BP (DBP) and 24-h average heart rate. The indexes of 24-h BP variability, diurnal and nocturnal, were calculated for both SBP and DBP (peripheral artery disease) as a s.d. below the mean of the measurements for the period considered and as indicated by the most recent guidelines.

Night/day ratio of BP was calculated as follows: mean nocturnal SBP/mean diurnal SBP. Using the night/day BP ratio as a continuous variable, the hypertensive subjects were classified in descending order from the highest degree of nocturnal BP fall (corresponding to the category of extreme dippers) to the lowest degree of nocturnal BP fall (corresponding to the category of reverse dippers). Patients classified according to this criterion were then divided into quartiles. The statistical analysis was performed by comparing the data of the upper quartile and the data of the lower quartile.

For the 24-h Holter ECG monitoring, Sorin Spiderview Digital Holter Recorder devices (Ela Medical, Sorin Group, Le Plessis Robinson, France) were used. The analysis of the data collected was performed with the ELA Medical SyneScope program, version 3.10.

The device was positioned between 0830 and 0930 h in the morning and worn by the patients for 24 h. Holter recording involves the placement of 7 to 10 electrodes in the precordial region. During monitoring, the patients were recommended to perform normal daily activities, while avoiding intense exercise.

The track was recorded in a special card contained in the device and then analyzed by the computer 3-channel recording.

The analysis, carried out by a single operator trained to use the software, initially distinguished between artifacts, normal beats and ventricular beats. Then, the operator's evaluation of the events were selected by the computer.

Holter ECG monitoring was considered invalid in the following cases: recording time <22 h; and number of artifacts and ectopic beats >20% of the total number of beats (in the presence of ectopic beats both the NN interval represented by the copula and the one represented by the postextrasystolic pause were excluded from the final analysis). The HRV study was performed in time domain measures during the day (7–23 h), during the night (23–7 h) and for 24 h.

Four time domain HRV parameters were calculated on the 24-h recording after excluding nonsinusal cardiac cycles:[10] the s.d. of all normal RR intervals (SDNN in ms) and the s.d. of the average normal RR intervals for all 5-min segments (SDANN in ms), reflecting long-term HRV and therefore mainly sympathetic activity or sympathovagal balance; the root mean square of the difference between the coupling intervals of adjacent RR intervals (rMSSD in ms); the percentage of adjacent RR intervals that varied by more than 50 ms (pNN50 in %), reflecting short-term beat-to-beat HRV and therefore mainly vagal activity; and the average of the s.d. of NN intervals calculated over 5 min (ASDNN/5 min).

Table 2 Time domain heart rate variability parameters—hypertensive subjects

Variable	Hypertensives (n = 125)
pNN50 24 h (%)	8.16 ± 10.2
pNN50 day (%)	6.76 ± 10.38
pNN50 night (%)	11.30 ± 12.96
RMSSD 24 h (ms)	37.91 ± 29.61
RMSSD day (ms)	34.91 ± 28.19
RMSSD night (ms)	42.42 ± 39.14
ASDNN/5 min 24 h (ms)	51.77 ± 21.48
ASDNN/5 min day (ms)	52.12 ± 31.82
ASDNN/5 min night (ms)	56.57 ± 30.61
SDANN/5 min 24 h (ms)	102.15 ± 35.40
SDANN/5 min day (ms)	74.85 ± 23.58
SDANN/5 min night (ms)	63.09 ± 26.43
SDNN 24 h (ms)	116.91 ± 36.27
SDNN day (ms)	92.61 ± 27.84
SDNN night (ms)	91.19 ± 37.05

Abbreviations: ASDNN, average of the s.d. of NN intervals; pNN50, percentage of adjacent RR intervals that varied by more than 50 ms; RMSSD, root mean square of the difference between the coupling intervals of adjacent RR intervals; SDANN, s.d. of the averaged normal RR intervals for all 5 min segments; SDNN, s.d. of NN intervals.
Data are presented as mean value ± s.d.

Holter examination and ABPM were performed sequentially in random order, and 53% of the patients underwent Holter examination first.

Statistical analysis

Statistical analysis of all quantitative and qualitative data, including descriptive statistics, was performed. Continuous data are expressed as the mean ± s.d., unless otherwise specified. Baseline differences between groups were assessed by the χ^2 test or Fisher's exact test as indicated for categorical variables. Univariate analysis of variance was performed for parametric variables, and *post hoc* analysis with the Bonferroni test was used to determine whether there were pairwise differences. Multinomial logistic regression analysis examined the relationship among different groups of patients (independent variables) and HRV indexes (dependent variable) in multiple regression models after adjustment for other variables that were significant in the univariate analysis. Odds ratios and their 95% confidence intervals were calculated. The data were analyzed with Epi Info software (version 6.0, Centers for Disease Control and Prevention, Atlanta, GA, USA) and IBM SPSS Software 21.0 version (SPSS, Chicago, IL, USA). All *P*-values were two sided, and *P*-values of <0.05 were considered statistically significant.

RESULTS

Table 1 shows the demographic and clinical variables of all of the enrolled hypertensives and of the controls. The controls differed significantly from hypertensives in the prevalence of diabetes and COPD (none of the controls were affected), anamnestic vascular damage, renal function, statin use and liver steatosis, but not in lipid profile, body mass index and waist circumference (see Table 1).

Table 2 shows the HRV parameters of all of the enrolled hypertensives.

In Table 3, the three rows of data illustrate demographic and clinical variables of the upper quartile and lower quartiles of hypertensives in relation to night/day SBP ratio compared with control subjects. Extreme dipper hypertensives were younger than reverse dippers (57.42 ± 11.04 *vs.* 69.0 ± 11.22 years) and had a shorter mean duration of hypertension (7.84 ± 8.86 *vs.* 17.10 ± 11.02 years). The two groups of hypertensives did not show significant differences regarding antihypertensive therapy. The reverse dippers showed poorer glycemic control than the extreme dippers (100.6 ± 22.54 *vs.* 122.6 ± 39.44). In

reverse dippers, we also observed a higher rate of anamnestic cerebral vascular events, the worst renal function, a higher waist circumference, a higher rate of left ventricular hypertrophy and a higher rate of bronchitis. In addition, 87% of the reverse dippers had liver steatosis (see Table 3).

The 24-h BP levels evaluated through ABPM (see Table 3) showed similar 24-h SBP and DBP levels in the two groups of hypertensives. During the day, SBP and DBP levels were higher in the upper quartile, whereas a significant difference was clearly seen during the night.

In Table 4, the time domain HRV parameters of the three groups are shown. The comparison of the upper and lower quartiles of night/day SBP ratio showed a significant difference in 24 h day and night SDNN and SDANN, indirectly showing a quite different degree of sympathetic activation throughout the 24-h period. It should be noted that, in our data, SDNN and SDANN of extreme dipper hypertensives were also greater than those of normotensive controls, although the difference was not statistically significant. When corrected for age, diurnal BP values, nocturnal BP values, waist circumference, anamnestic vascular events, differences in renal function, COPD, liver steatosis and left ventricular hypertrophy maintained statistical significance (see the multinomial logistic regression upper *vs.* lower quartiles of night/day SBP ratio, Table 5).

For the pNN50 and RMSSD levels, reflecting parasympathetic tone, the data did not show any significant variations among the three groups, and this is similar to what has been shown in other studies.

DISCUSSION

The results of our study performed in subjects affected by essential hypertension and receiving antihypertensive and, for some subjects, metabolic therapies, provide, in our opinion, some elements that should be highlighted and raise some new issues:

(1) As has been shown by other authors, our results confirm that the worst clinical features and the highest rate of organ damage and comorbidities are associated with the reverse dipper profile compared with the other categories of night/day BP ratio.
(2) Our results also appear to confirm a linear relationship between the reduction of the night/day ratio and the increase of sympathetic tone, extending it even to the extreme dipper profile that had lower levels of sympathetic tone with respect to the reverse dipper profile and also compared with the control group. This relationship remained after adjustment for all possible confounders.
(3) Our findings confirm the substantial absence of changes in parasympathetic tone in relation to the different sleep/wake profiles.
(4) To the best of our knowledge, our data provide the first evidence that extreme dipper hypertensives have a sympathovagal balance similar to that of normotensive controls.

Our results confirm the hypothesis that reverse dipper hypertensives have a decreased physiological circadian fluctuation of autonomic functions compared with extreme dippers and normotensives. Our results also confirm that reverse dipper hypertensives have the worst amount of organ damage; the worst clinical profile being the subgroup with the longest duration of hypertension; the worst renal function and glycemic control; the largest abdominal circumference; and the greatest prevalence of hepatic steatosis, COPD and left ventricular hypertrophy. The analysis of time domains of HRV revealed a significant reduction of SDANN and SDNN indexes in this group during the daytime, nighttime and 24-h period. SDANN and SDNN

Table 3 Demographic and clinic variables—ABPM data of hypertensive subjects upper *vs.* lower quartile of night/day SBP ratio

Variable	Quartile top (T) (n = 31)	Quartile bottom (B) (n = 31)	Controls (C) (n = 30)	P-value
M/F, *n* (%)	20/11 (64.52/35.48)	12/19 (38.71/61.29)	16/14 (53.33/46.67)	
Age (years)	57.42 ± 11.04	69.0 ± 11.22	42.13 ± 14.01	0.0005
				0.0005 T *vs.* C[a]
				0.0005 B *vs.* C[a]
				0.001 T *vs.* B[a]
Duration of hypertension (years)	7.84 ± 8.86	17.10 ± 11.02	—	0.001
Achievement of BP target, *n* (%)	8 (25.8%)	11 (35.5%)	—	0.01
Type of drugs assumed, n *(%)*				
ACEis	3 (9.7%)	5 (16.1%)		0.707
ARBs	19 (61.3%)	17 (54.8%)		0.797
Diuretics	8 (25.8%)	8 (25.8%)	—	0.780
CCBs	10 (32.3%)	8 (25.8%)		1.000
β-Blockers	7 (22.6%)	13 (41.9%)		0.174
Other (α-blockers, clonidine)	3 (9.7%)	6 (19.3%)		0.473
Mean number of drugs assumed, per patient	1.5	1.6	—	0.740
Current smokers, *n* (%)	10 (32.3%)	6 (19.3%)	6 (38.1%)	0.384
Past smokers, *n* (%)	6 (10.3%)	5 (16.1%)	2 (9.5%)	1.000
Diabetes (*n*/%)	7 (22.6%)	14 (45.2%)	0	0.106
Fasting glucose (mg dl^{-1})	100.6 ± 22.54	122.6 ± 39.44	85.03 ± 8.49	0.0005
				0.0005 B *vs.* T[a]
				0.005 B *vs.* C[a]
Past cerebral vascular event, *n* (%)	2 (6.4%)	11 (35.5%)	0	0.011
Past cardiac vascular event, *n* (%)	5 (16.1%)	12 (38.7%)	0	0.086
Past peripheral arterial disease, *n* (%)	2 (6.4%)	6 (19.3%)	0	0.255
Creatinin (mg dl^{-1})	0.90 ± 0.31	1.05 ± 0.41	0.79 ± 0.15	0.005
				0.004 B *vs.* C[a]
Cr Cl (ml min^{-1})	99.1 ± 30.55	66.9 ± 34.14	127.38 ± 34.74	0.0005
				0.0005 B *vs.* C[a]
				0.004 T *vs.* C[a]
				0.001 T *vs.* B[a]
Statin use, *n* (%)	15 (48.4%)	15 (48.4%)	1 (3.3%)	1.000
BMI	27.7 ± 3.77	29.0 ± 5.47	28.2 ± 4.52	0.543
Waist circumference (cm)	98.1 ± 9.61	104.4 ± 12.84	97.3 ± 8.59	0.018
				0.029 B *vs.* C[a]
Liver steatosis, *n* (%)	18 (58.1%)	27 (87.1%)	6 (20.0%)	0.0005
				0.022 T *vs.* B[a]
				0.005 T *vs.* C[a]
				0.0005 B *vs.* C[a]
COPD (*n*/%)	0	6 (19.3%)	0	0.024
Total cholesterol (mg dl^{-1})	189.2 ± 50.52	174.6 ± 49.66	203.8 ± 35.24	0.052
HDL cholesterol (mg dl^{-1})	48.7 ± 10.17	44.68 ± 15.45	46.3 ± 8.16	0.405
Triglycerides (mg dl^{-1})	122.2 ± 60.92	137.0 ± 58.04	118.93 ± 48.54	0.409
Left ventricular hypertrophy, *n* (%)	1 (3.1 %)	8 (25.8%)	0	0.001
Night/day SBP ratio	0.7935 ± 0.036	1.045 ± 0.038	0.859 ± 0.073	0.001
24-h SBP (mm Hg)	129.8 ± 10.56	132.1 ± 14.79	108.66 ± 27.35	0.0005
				0.0005 B *vs.* C[a]
				0.0005 T *vs.* C[a]
24-h DBP (mm Hg)	76.4 ± 7.96	72.2 ± 9.57	70.40 ± 4.18	0.008
				0.008 T *vs.* C[a]
24-h HR (b.p.m.)	68.93 ± 9.71	68.34 ± 8.20	74.31 ± 7.24	0.013
				0.045 T *vs.* C[a]
				0.021 B *vs.* C[a]
Day SBP (mm Hg)	138.32 ± 11.24	130.39 ± 14.58	120.96 ± 8.02	0.0005
				0.026 T *vs.* .B[a]
				0.0005 T *vs.* C[a]
				0.006 B *vs.* C[a]
Day DBP (mm Hg)	81.80 ± 8.56	72.02 ± 9.87	74.09 ± 4.66	0.0005
				0.0005 B *vs.* T[a]
				0.001 T *vs.* C[a]

Table 3 (Continued)

Variable	Quartile top (T) (n = 31)	Quartile bottom (B) (n = 31)	Controls (C) (n = 30)	P-value
Day HR (b.p.m.)	72.2 ± 10.82	69.6 ± 8.53	79.13 ± 8.40	0.0005
				0.015 T vs. C[a]
				0.0005 B vs. C[a]
Night SBP (mm Hg)	109.6 ± 8.23	136.45 ± 16.33	103.04 ± 9.87	0.0005
				0.0005 B vs. T[a]
				0.0005 B vs. C[a]
Night DBP (mm Hg)	64.1 ± 7.77	72.4 ± 9.77	62.38 ± 6.31	0.0005
				0.0005 B vs. T[a]
				0.0005 B vs. C[a]
Night HR (b.p.m.)	61.03 ± 8.34	65.85 ± 9.90	63.55 ± 6.72	0.086
s.d. 24 h SBP (mm Hg)	22.83 ± 5.05	17.80 ± 3.79	18.30 ± 4	0.0005
				0.0005 T vs. B[a]
				0.0005 T vs. C[a]
s.d. 24 h DBP (mm Hg)	17.44 ± 4.80	13.35 ± 2.60	14.62 ± 3.56	0.0005
				0.013 T vs. C[a]
				0.0005 T vs. B[a]
s.d. 24 h HR (mm Hg)	14.04 ± 9.99	8.44 ± 2.90	15.67 ± 5.14	0.0005
				0.0005 T vs. C[a]
				0.004 T vs. B[a]
s.d. day SBP (mm Hg)	20.17 ± 6.61	18.27 ± 4.43	17.73 ± 4.01	0.156
s.d. day DBP (mm Hg)	16.88 ± 6.17	14.04 ± 2.68	14.92 ± 4.32	0.052
s.d. night SBP (mm Hg)	13.23 ± 3.23	14.63 ± 3.77	10.46 ± 3.04	0.0005
				0.006 T vs. C[a]
				0.0005 B vs. C[a]
s.d. night DBP (mm Hg)	10.03 ± 3.81	10.02 ± 4.14	8.28 ± 2.64	0.1

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; Cr Cl, creatinine clearance; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; M/F, male/female; PAD, peripheral artery disease; SBP, systolic blood pressure.
Creatinine clearance has been calculated through Cockroft and Gault formula.
Data are presented as mean value ± s.d.
[a]Post hoc analysis with the Bonferroni test.

represent indexes that estimate long-term components of HRV; therefore, they have a good stability and reproducibility that renders the results more reliable.[10]

Our data are consistent with the findings of previous studies, such as data reporting that reverse dippers appear to have the highest level of sympathetic activity (measured directly in the peroneal nerve) among all hypertensive patients;[11] data provided from evaluations by Kohara et al.[13] indicating that nondipper and reverse dipper hypertensive subjects are characterized by a decreased physiological circadian fluctuation on autonomic functions (valued by power spectral analysis of heart rate variability) compared with dipper subjects; and similar findings provided by Salles et al.[14] obtained in subjects affected by resistant hypertension already under multiple pharmacological therapy.

In our study, we decided to use time domain HRV indexes for the analysis of 24-h ambulatory ECG monitoring because the lower stability of heart rate modulations during long-term recordings makes the results of frequency methods less easily interpretable.[10]

When compared with the lower quartile, the upper quartile (extreme dippers) showed a significant increase in nocturnal, diurnal and 24-h SDANN and SDNN, without any differences in pNN50 and RMSSD, the indexes that estimate the short-term components of HRV and correlate best with the parasympathetic activity.[10]

The best homeostasis of sympathovagal balance observed in extreme dippers, which was similar to that in normotensive controls, may serve a protective role, thus leading us to reconsider what the real prognosis of extreme dipper patients might be. In fact, in our sample, extreme dippers presented with the shortest-duration hypertension, the best

renal function, the fewest past vascular events and the lowest rate of comorbidities. In fact, the prognosis of this category of hypertensives is still under discussion: some studies have demonstrated a similar prognosis in nondipper and extreme dipper subjects, assigning a worse prognosis to both subgroups compared with dipper patients.[7,23] A study by Yano and Kario[24] has emphasized the potential heterogeneity of the extreme dipper category according to the different grades of sympathetic activation identified by morning surge. However, other authors do not share this point of view: Kansui et al.,[25] studying a sample of 100 subjects with resistant hypertension, have found that only 3 of these had an extreme dipper profile, whereas 77 were mild dippers or risers. Fagard[1] has reported that in hypertensive patients without previous cardiovascular events, the mortality is lower in extreme dippers compared with dippers. Even Fagard et al.,[9] in a large meta-analysis exploring the prognostic significance of the night/day BP ratio, have reported a lower mortality in extreme dipper hypertensives than in dippers (the same meta-analysis showed the highest mortality in reverse dippers and a similar cardiovascular risk between dippers and nondippers, thus underlying the need to divide hypertensives using four dipping categories separately to provide the optimal prognostic value).

One of the main negative prognostic elements attributed to extreme dipper hypertensives, especially older extreme dippers, is an excess of silent cerebrovascular events.[8] This finding, therefore, may not necessarily be linked to an impaired sympathovagal balance and/or to the presence of exaggerated sympathetic nerve activity, but instead may be because of the exaggerated difference between night and day BP, with the possible occurrence of nocturnal hypoperfusion

Table 4 Time domain heart rate variability parameters of the hypertensive subjects upper *vs.* lower quartile of night/day SBP ratio

Variable	Quartile top (T) (n = 31)	Quartile bottom (B) (n = 31)	Controls (C) (n = 30)	P-value
HR 24 h (b.p.m.)	71.0 ± 9.76	69.1 ± 9.59	75.56 ± 8.7	0.027
				0.027 B *vs.* C[a]
HR day (b.p.m.)	76.3 ± 11.51	71.7 ± 11.10	82.24 ± 9.61	0.001
				0.001 B *vs.* C[a]
HR night (b.p.m.)	61.8 ± 9.62	65.3 ± 9.68	65.09 ± 8.64	0.229
pNN50 24 h (%)	8.37 ± 8.58	9.2 ± 12.92	11.20 ± 9.73	0.567
pNN50 day (%)	6.04 ± 7.51	8.32 ± 13.64	7.96 ± 7.64	0.631
pNN50 night (%)	13.48 ± 14.78	10.75 ± 13.10	18.06 ± 18.47	0.187
RMSSD 24 h (ms)	42.93 ± 40.87	38.84 ± 30.61	39.95 ± 21.00	0.874
RMSSD day (ms)	33.91 ± 30.08	39.73 ± 32.77	32.75 ± 15.93	0.566
RMSSD night (ms)	56.12 ± 65.37	39.96 ± 28.40	48.08 ± 32.65	0.378
ASDNN/5 min 24 h (ms)	59.43 ± 25.11	49.62 ± 22.27	60.48 ± 19.44	0.117
ASDNN/5 min day (ms)	54.24 ± 18.94	48.27 ± 22.04	56.58 ± 17.21	0.234
ASDNN/5 min night (ms)	69.72 ± 44.98	53.47 ± 25.21	61.50 ± 30.98	0.190
SDANN/5 min 24 h (ms)	130.21 ± 33.11	76.46 ± 24.33	121.95 ± 30.35	0.0005
				0.0005 B *vs.* T[a]
				0.0005 B *vs.* C[a]
SDANN/5 min day (ms)	82.87 ± 24.97	62.22 ± 17.86	75.82 ± 18.61	0.001
				0.001 T *vs.* B[a]
				0.037 B *vs.* C[a]
SDANN/5 min night (ms)	75.3 ± 30.74	53.94 ± 19.89	66.21 ± 21.08	0.004
				0.003 T *vs.* B[a]
SDNN 24 h (ms)	145.07 ± 36.27	94.30 ± 26.77	136.34 ± 33.34	0.0005
				0.0005 B *vs.* C[a]
				0.0005 B *vs.* T[a]
SDNN day (ms)	101.95 ± 27.84	82.26 ± 25.81	96.17 ± 23.15	0.011
				0.011 T *vs.* B[a]
SDNN night (ms)	111.89 ± 37.05	80.66 ± 26.75	98.47 ± 33.01	0.005
				0.004 T *vs.* B[a]

Abbreviations: ASDNN, average of the s.d. of NN intervals; HR, heart rate; pNN50, percentage of adjacent RR intervals that varied by more than 50 ms; RMSSD, root mean square of the difference between the coupling intervals of adjacent RR intervals; SBP, systolic blood pressure; SDANN, s.d. of the averaged normal RR intervals for all 5 min segments; SDNN, s.d. of NN intervals.
Data are presented as mean value ± s.d.
[a]*Post hoc* analysis with the Bonferroni test.

Table 5 Multinomial logistic regression upper *vs.* lower quartile of N/D SBP ratio

Variable	OR (95% CI)	P-value
SDANN 24 h (ms)	1.079 (1.029–1.132)	0.002
SDANN day (ms)	1.128 (1.042–1.220)	0.003
SDANN night (ms)	1.038 (0.998–1.080)	0.064
SDNN 24 h (ms)	1.098 (1.039–1.161)	0.001
SDNN day (ms)	1.074 (1.026–1.124)	0.002
SDNN night (ms)	1.045 (1.004–1.088)	0.031

Abbreviations: CI, confidence interval; N/D, night/day; OR, odds ratio; SBP, systolic blood pressure; SDANN, s.d. of the averaged normal RR intervals for all 5 min segments; SDNN, s.d. of NN intervals.
Values are adjusted for all the other variables that resulted significant at univariate analysis.

(furthermore, these patients at night have similar levels of SBP and DBP to those of normotensive controls), particularly when antihypertensive therapy is administered without prior establishment of the nocturnal BP profile of the patient.[6,26] The peculiar circadian rhythm of BP of this subgroup of hypertensives may create conditions for the occurrence of nocturnal hypotension or might further accentuate of the early morning surge of BP that is already known to occur in these patients.[27]

Another issue that emerges from the analysis of our findings is that the absence of sympathetic overactivation in the extreme dipper profile seems to bring into question the common belief that essential hypertension is sustained by sympathetic overactivation. Several authors[28,29] have underlined the role of increased sympathetic activity in the pathogenesis of essential hypertension, particularly in the early stage, assuming that, with the progression of the hypertensive disease, a transition occurs from a 'hyperkinetic state' to a high-resistance condition with downregulation of β-adrenergic receptors with a secondary normalization of the sympathetic tone. This assumption seems to be inconsistent with what has been shown by other authors who have identified a gradual increase in sympathetic tone with the increase in the night/day ratio of systolic blood pressure (9–12), a typical feature of elderly patients with a longer duration of hypertension and major comorbidities. Furthermore, a recent systematic review[30] has highlighted that although several studies have demonstrated an autonomic dysfunction in hypertensives, there are no data establishing the proportion of hypertensive subjects who exhibit signs of excessive sympathetic tone because it is not likely that all patients have sympathetic overactivation. DiBona and Esler[31] have estimated that patients with essential hypertension and sympathetic activation may represent 50% of all hypertensives.

In this context, our research does not seem to confirm previous reports regarding young healthy normotensive subjects[32] in whom a greater nocturnal BP fall has been associated with higher levels of muscle sympathetic nerve activity. It should be emphasized that, in this study of normotensives, the mean nocturnal fall of the higher

tertile was only 13.0 *vs.* 8.3% in the first tertile, therefore not representing the extreme dipper population.

Another possible explanation of our findings may be associated with the features of some extreme dippers, one of which may be the quality of rapid eye movement sleep in these patients. It is possible to hypothesize that the extreme dippers, being younger, might have better homeostasis of the sympathovagal balance during the night. This phenomenon could be because of a higher proportion and/or quality of rapid eye movement sleep that is the stage with higher alterations between the two autonomic components. This would lead, inevitably, to an increase in the variability of the cardiac rate and an increased in BP variability, as confirmed by data collected in such patients by our group. The above condition may explain the characteristics of the BP nocturnal profile in these patients that change physiologically with age or with the onset of pathological conditions such as diabetes mellitus, heart failure or ischemic heart disease.[33]

A possible limitation of our study is that we performed the ECG Holter monitoring and ABPM during pharmacological treatment, but this approach was primarily used for ethical reasons. There were no differences regarding the antihypertensive treatments between the two quartiles analyzed (see Table 4). Moreover, the influence of drugs (antihypertensive and metabolic) on the activity of the autonomic nervous system has not led to an unambiguous result in the literature. Differences exist in terms of action for entire classes of drugs and for single molecules.[30] These reported differences could be because of the different pharmacodynamic and/or pharmacokinetic properties of the single molecules, the basic properties of the drugs and the different research techniques used in various studies.[34] Regarding β-blockers, while considering the differences between the different molecules, doses and schedules of administration, several authors have shown the ability of these molecules to modulate the activity of the autonomic nervous system, reducing sympathetic tone and increasing vagal tone after β-blockade.[35] However, a study by Burns *et al.*[36] evaluating the effects of therapy with atenolol has shown that the activity of the SNS is not substantially different between treated subjects and the untreated controls. Furthermore, even assuming that the modulation of the autonomic nervous system demonstrated by β-blockers in patients with congestive heart failure and ischemic heart disease also occurs in all the hypertensives, our data showed a significant increase of SDANN and SDNN in extreme dippers, although in our study 41.9% of reverse dippers were treated with β-blockers. On one hand, this could be an indication of the relative ineffectiveness of β-blockade in patients with multiple stimuli to increase sympathetic tone and, on the other hand, this could emphasize how an increase in sympathetic tone may not be a universal characteristic among all hypertensives.

Another possible limitation is that, in a sample such as ours, the decreased HRV in long-term components observed in reverse dipper hypertensives may be attributed to a reduction in vagal tone and an increase in sympathetic activity that is physiologically associated with advancing age[10] and with pathologies such as diabetes mellitus, congestive heart failure, COPD[37] and ischemic heart disease that are usually associated with reverse dipper profiles.[20] However, considering the actual differences between the two quartiles, the multinomial logistic regression analysis confirmed the significant differences in the HRV parameters that are indicative of a different extent of sympathetic activation.

In conclusion, our study provides further elements that may be useful to identify the sympathovagal balance of hypertensives in relation to the night/day BP ratio. Our main finding is that a different degree of adrenergic activity was encountered between extreme and reverse dippers. The preservation of homeostasis of sympathovagal balance in extreme dippers, having fewer comorbidities and lower cardiovascular risk, could

therefore play a protective role for these subjects, ensuring a prognosis that is at least similar to and not worse than that of dippers. The assessment of the prognosis of extreme dipper hypertensives is a subject that is not expressly addressed in this paper; considering our results, this topic deserves greater attention in the future. Here, we have determined that reverse dippers have the worst outcomes, but further studies are needed to clarify the real prognostic value for extreme dippers. In addition, stratifying the patients by age (do the young extreme dippers have a better prognosis than the old ones?) and morning surge levels (how relevant is the presence or absence of an exaggerated morning surge of BP in these patients?) should be beneficial in future studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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