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ORIGINAL ARTICLE

Autonomic nervous system activity is independently associated with the risk of shift in the non-dipper blood pressure pattern

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An insufficient decrease in nocturnal blood pressure (BP) is a known factor in cardiovascular mortality. We aimed to determine whether autonomic nervous system (ANS) activity and its change over 2 years were associated with a shift to non-dipper status, independently of initial BP, in a general elderly population. From participants in the PROOF study, 600 subjects untreated for hypertension were selected (age at baseline: 65 years, men: 41.5%). Dipper/non-dipper status was defined using repeated measures of 24-h ambulatory BP at baseline and 2 years later. ANS activity was evaluated on the basis of 24-h heart rate variability at both examinations. Among the 454 dipper subjects at baseline, 26.2% became non-dippers. Multivariate analysis showed that a +1 between-subject s.d. increase in the very low frequency at baseline was associated with a decreased odds ratio for the shift to non-dipper status 2 years later (OR=0.61 [0.41–0.91], *P*=0.02). The within-subject change between the two measurements of day and night systolic BP and day diastolic BP also contributed significantly to the risk of shift to non-dipper status. Our results suggest that impaired ANS activity precedes an insufficient decrease in nocturnal BP independent of hypertension status.
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INTRODUCTION

An insufficient decrease in nocturnal blood pressure (BP) (non-dipping) is recognized as a marker of end-organ damage and a predictor of cardiovascular and all-cause mortality, independently of hypertension status.[1–3] Our understanding of the pathophysiologic factors that may be involved in the mechanisms of the circadian variation of BP and the non-dipping pattern remains incomplete. Among the suspected determinants, autonomic nervous system (ANS) activity is shown to be associated with arterial BP level and involved in the control of the circadian variation of BP.[4,5] Previous cross-sectional studies have shown that ANS activity, evaluated by heart rate variability (HRV), was reduced in non-dipper, untreated hypertensive subjects.[6,7] A possible explanation of the nocturnal decrease in BP is that it results from a reduction of sympathetic nervous activity and impaired circadian rhythm in sympatho-vagal balance during sleep.[8,9]

We aimed to assess whether ANS activity indices and their changes over 2 years, as evaluated by 24-h HRV, were associated with a shift to non-dipper status among subjects identified as dippers at study entry in a general elderly population not treated for hypertension.

METHODS

Study population

This study sample was selected from participants in the PROOF study, a prospective observational cohort of 1011 age-matched subjects at baseline. The PROOF study was designed to assess the prognostic values of ANS activity in cardiovascular morbidity and mortality. The population included subjects selected from an electoral list of 65-year-old people living in the town of Saint-Etienne, France, in 2001. The design of the PROOF study has been previously published.[10]

In this study, we excluded subjects who were being treated for hypertension at inclusion (with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers, diuretics, calcium channel blockers or other antihypertensive drugs). This information was collected through subjects' self-report and confirmed by physicians' prescriptions. We also excluded subjects with inconsistent or missing HRV or BP measurements.

Examination procedure

Baseline examinations were performed between January 2001 and December 2002 at the University Hospital in Saint-Etienne, France. The second examination was performed between January 2003 and December 2004. An interval of

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2 years between the two examinations was ensured for every subject. The protocol of the PROOF study was approved by the institutional research program (National Hospital Program for Clinical Research) and by the local ethics committee (CPPRB Rhône-Alpes Loire, France). All subjects gave informed written consent.

HRV measurements

HRV was measured at each examination using a 24-h electrocardiographic Holter system (Ultima, Duosoft, Novacor, Rueil-Malmaison, France) that allows extraction of the list of RR intervals with a precision of 0.008 s. Each RR interval was manually validated before analysis. HRV was assessed by analyzing RR intervals according to the frequency of the signal represented by successive RR intervals. RR intervals free of arrhythmias were individually selected for HRV analysis.

Frequency domain indices and mean heart rate were calculated as recommended.[11] All the calculated indices are recognized to provide a reliable estimate of ANS activity.[12]

Among the frequency indices, we analyzed the total frequency power, the high-frequency (HF) peak, the low-frequency (LF) peak, the very-low-frequency (VLF) peak, the ultra-low-frequency peak and the sympathetic balance at night, defined as the ratio LF/HF.

Ambulatory BP monitoring and hypertension status

Twenty-four-hour ambulatory BP monitoring (ABPM) was assessed at each examination by ambulatory Holter recordings using an auscultatory method (Diasys Integra, Novacor, Rueil-Malmaison, France). The measurements were programmed to be recorded every 15 min during the day and every 30 min during the night, with the cuff placed on the non-dominant arm. Average values of systolic and diastolic BP were calculated for the different recording periods: day, night and 24 h. The daytime interval was from 0700 to 2200 hours and the nighttime interval from 2200 to 0700 hours. Hypertensive status was defined as 24-h ABPM $\geqslant$130/80 mm Hg.[13]

Circadian variations of ABPM and non-dipper status

The circadian variation of BP was defined as the ratio of the difference between the day and night systolic measurements to the day systolic measurements. The non-dipper pattern was defined at each examination as a decrease in nocturnal systolic ABPM values of $<$10% relative to diurnal measurement.[14] The circadian variations of BP after 2 years were studied in quartiles.

Using the two measurements of ABPM, taken with an interval of 2 years, we identified four groups: non-dipper subjects who remained non-dippers 2 years later, non-dipper subjects who became dippers, dippers who remained dippers and dippers who became non-dippers.

Clinical covariates

Several potential confounding factors, identified at inclusion, were considered: gender, body mass index, self-reported smoking status, fasting glycemia, total cholesterol and score on the abnormal autonomic sleep fragmentation index, an index of sleep-related breathing disorders.[15–17] In addition, information regarding introduction of an antihypertensive treatment (angiotensin-converting enzyme or angiotensin-receptor blocker, β-blockers, diuretics, calcium channel blockers or other antihypertensive drugs) between the two examinations was collected at the second examination.

Statistical analysis

The subjects' characteristics were compared among the four groups according to the dipper/non-dipper status at both examinations to identify potential between-subject differences, using Pearson's χ^2 and Fisher's test of ANOVA models as appropriate.

Mean values of the HRV indices and heart rate were compared among the groups using a multivariate ANOVA adjusted for potential confounders. A logarithmic transformation was performed on the HRV indices because their distributions were skewed. The Bonferroni's method was used as a *post hoc* test to adjust the level of significance for multiple pair-wised comparisons.

Univariate logistic regression models were used to determine whether the ANS activity indices at baseline of the subjects who were dippers at inclusion and their changes between the two examinations were associated with a shift to non-dipper status. The day and night systolic and diastolic BP readings and their change over 2 years were also included in the models.

The variables that were significantly associated with the risk of shift to non-dipper status in the univariate models were included in a multivariate step-wise logistic regression.

The within-subject changes of the ANS activity indices between the two examinations were analyzed by categories: a decrease of at least 10%, an increase of at least 10% and the middle category as reference.

A similar analysis was conducted among the non-dipper subjects at inclusion to identify which indices were associated with a shift in dipping status 2 years later.

We also compared the ANS indices between the quartiles of the circadian variation of BP at 2 years. This was to ensure the consistency of our findings and address the potential lack of reproducibility of non-dipper status.[18,19]

Values were expressed as percentage (number of subjects), mean (s.d.) or odds ratio (confident interval at 95%). Data were analyzed using the SPSS statistical software package 12.0 for Windows (SPSS Software, Chicago, IL, USA).

RESULTS

Of the 1011 subjects initially included in the PROOF study, 786 (77.7%) were not treated for hypertension. Baseline data were incomplete for 46 subjects; in addition, data were missing for 140 subjects after 2 years of follow-up. The study population consisted of 600 subjects who were present at the two examinations. Among them, 454 were considered dippers.

After 2 years of follow-up, 119 (26.2%) of the 454 dipper subjects at baseline had shifted to non-dippers, and 71 (48.6%) of the 146 non-dipper subjects at baseline had shifted to dippers (Table 1). The subjects' characteristics were statistically significant for day and night BP at baseline and 2 years later, according to dipper/non-dipper status at the two examinations. Day systolic and diastolic BP was higher among the dippers at baseline in comparison with the non-dippers, whereas night values were lower. This held true 2 years later when the same groups were compared.

Without reaching statistical significance, the proportion of men tended to be higher among the non-dippers who became dippers compared with the other groups ($P=0.08$).

The group of dipper subjects at inclusion who became non-dippers 2 years later had baseline HF, LF and VLF indices significantly lower than the other groups, especially in comparison with the group of dipper subjects who remained dippers (Table 2). The tendency for the other indices was similar even though statistical significance was not reached. There was no significant difference between the group of dipper subjects who remained dippers and the group of non-dipper subjects who remained non-dippers according to the *post hoc* tests.

Among the dipper subjects at inclusion, the univariate analyses showed that increases in HF, LF and VLF at baseline were associated with lower odds ratios for the shift to non-dipper status 2 years later (Table 3). An increase of at least 10% of VLF and LF between the two examinations contributed to the shift to non-dipper status 2 years later.

In the multivariate step-wise logistic regression model, the role of baseline VLF remained significant (Table 3). Of note, a within-subject increase of at least 10% in day BP (systolic or diastolic) was associated with a reduced risk of shift to non-dipper status, whereas the same increase in night systolic BP increased this risk (OR=7.62). On the contrary, a within-subject decrease of at least 10% in day systolic BP was associated with a higher risk of shift to non-dipper status (OR=3.70), whereas the same decrease of night systolic BP carried a lower risk (OR=0.15).

Table 1 Descriptive characteristics at baseline and 2 years later of study population according to dipper/non-dipper status

	D1/D2 (n=335)		*D1/ND2 (n=119)*		*ND1/D2 (n=71)*		*ND1/ND2 (n=75)*		*(Fisher's test)*	*Total (n=600)*	
	Mean	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*	P	*Mean*	*s.d.*
Age (years)	65.63	0.74	65.70	0.91	65.74	0.93	65.70	0.82	0.64	65.69	0.81
BMI ($kg\,m^{-2}$)	24.90	3.24	24.90	3.52	24.68	3.27	24.62	3.60	0.89	24.78	3.34
Total cholesterol ($mmol\,l^{-1}$)	6.15	0.99	6.02	0.99	6.04	0.83	6.18	1.04	0.53	6.10	0.98
Fasting glycemia ($mmol\,l^{-1}$)	5.56	0.87	5.62	1.03	5.41	1.47	5.34	1.13	0.19	5.48	1.02
24-h systolic ambulatory BP at baseline	117.56	13.14	117.98	13.00	116.87	13.90	115.39	14.20	0.57	117.29	13.33
24-h diastolic ambulatory BP at baseline	75.57	7.49	75.72	7.74	75.33	7.21	75.07	8.28	0.94	75.51	7.60
Day systolic ambulatory BP at baseline	123.44	13.66	123.20	13.58	119.14	14.12	117.24	14.26	0.001	122.12	13.93
Day diastolic ambulatory BP at baseline	79.08	7.71	78.81	8.19	76.99	7.67	76.73	8.42	0.042	78.49	7.93
Night systolic ambulatory BP at baseline	100.37	12.27	102.63	12.72	110.94	13.63	110.00	14.11	<0.001	103.26	13.39
Night diastolic ambulatory BP at baseline	65.51	7.82	66.72	8.14	70.89	7.33	70.47	8.72	<0.001	67.00	8.21
24-h systolic ambulatory BP 2 years later	117.79	13.33	117.73	13.22	117.29	12.82	116.08	14.20	0.79	117.50	13.34
24-h diastolic ambulatory BP 2 years later	74.31	6.97	72.81	6.70	74.66	8.22	73.46	7.86	0.19	73.95	7.20
Day systolic ambulatory BP 2 years later	123.49	14.08	119.23	13.60	122.17	14.03	117.38	14.33	0.001	121.73	14.17
Day diastolic ambulatory BP 2 years later	77.79	7.39	74.59	7.01	77.39	8.52	74.81	7.64	<0.001	76.74	7.61
Night systolic ambulatory BP 2 years later	101.59	12.61	113.70	13.41	102.96	12.03	112.70	15.55	<0.001	105.53	14.14
Night diastolic ambulatory BP 2 years later	64.32	7.16	68.28	7.40	66.51	8.28	69.65	9.95	<0.001	66.02	8.00
	Percentage	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*(Pearson's χ^2)*	*Percentage*	n
Men	43.28	145	36.97	44	50.70	36	32.00	24	0.08	41.50	249
Smoker	5.37	18	5.04	6	15.49	11	6.67	5	0.02	6.67	40
ASF index	37.01	124	35.29	42	38.03	27	40.00	30	0.93	37.17	223
Hypertensives at baseline	23.88	80	17.65	21	16.90	12	22.67	17	0.38	21.67	130
Hypertensives 2 years later	19.10	64	21.85	26	23.94	17	17.33	13	0.69	20.00	120
Hypertensive treatment 2 years later	27.16	91	29.41	35	23.94	17	30.67	23	0.79	27.67	166

Abbreviations: ASF, autonomic sleep fragmentation; BMI, body mass index; BP, blood pressure; D1, ND1, dipper, non-dipper at baseline; D2, ND2, dipper, non-dipper after 2 years.

Table 2 Autonomic nervous system activity characteristics at baseline of the study population according to the dipper/non-dipper status, using two measurements (means adjusted for hypertensive status at baseline)

	D1/D2		*D1/ND2*		*ND1/D2*		*ND1/ND2*		*(Fisher's test)*	*Total*	
	Mean	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*	P	*Mean*	*s.d.*
In 24-h HF	4.62	0.81	4.39	0.79	4.66	0.95	4.72	0.92	0.03	4.60	0.84
In 24-h LF	5.40	0.63	5.18	0.71	5.40	0.67	5.27	0.78	0.02	5.31	0.67
In 24-h VLF	6.39	0.57	6.18	0.65	6.43	0.55	6.32	0.66	0.005	6.33	0.60
In 24-h ULF	7.77	0.60	7.69	0.69	7.76	0.60	7.79	0.61	0.65	7.77	0.62
In 24-h Ptot	8.17	0.53	8.05	0.63	8.17	0.52	8.16	0.59	0.24	8.14	0.56
In night LF/HF	0.98	0.63	0.98	0.71	0.98	0.71	0.84	0.63	0.36	0.95	0.66
In 24-h HR	6.73	0.11	6.71	0.11	6.75	0.11	6.74	0.12	0.07	6.73	0.11

Abbreviations: D1, ND1, dipper, non-dipper at baseline; D2, ND2, dipper, non-dipper after 2 years; HF, high frequency; LF, low frequency; Ptot, total frequency power; ULF, ultra-low frequency; VLF, very low frequency.

Among the dipper subjects at inclusion, the quartiles of the circadian variation of BP at 2 years were determined with the thresholds of 9.6, 14.9 and 19.4.The subjects in the fourth quartile (lower than 9.6) tended to have lower baseline ANS indices than those in the second (between 9.6 and 14.9) and third (between 14.9 and 19.4) quartiles. Differences were significant for LF and VLF (Figures 1 and 2). Adjustment for covariates did not modify this relationship. The mean baseline ANS activity indices were similar for the first (higher than 19.4) and fourth quartiles.

Among the non-dipper subjects at inclusion, the risk of shift to dipper status was not significantly associated with the ANS activity indices: LF (OR=1.29 [0.82–2.03], *P*=0.28), VLF (OR=1.36 [0.27–1.36], *P*=0.27) or HF (OR=0.94 [0.66–1.34], *P*=0.73) at baseline. The introduction of an antihypertensive treatment between the two examinations did not contribute to this shift (*P*=0.63).

DISCUSSION

In this study, we investigated the association between ANS activity, its change over 2 years and the risk of shift to non-dipper status 2 years later in an untreated elderly study population. About 32% of the subjects changed status—from dipper to non-dipper or vice versa—2 years later, which is similar to Omboni *et al*.'s[18] result (40%) at 1 year of follow-up among exclusively hypertensive subjects who were younger than our subjects.

Table 3 Univariate and multivariate analyses of the association between the autonomic nervous system activity indices and the non-dipper status after 2 years of follow-up, among the dippers at inclusion (*n*=454)

	OR	*CI=95%*		P
Univariate models				
Indices at baseline				
In 24-h HF	0.74[a]	0.54	0.96	0.02
In 24-h LF	0.63[a]	0.46	0.87	0.005
In 24-h VLF	0.58[a]	0.41	0.83	0.003
Day ambulatory systolic BP	1.00[a]	0.98	1.01	0.83
Day ambulatory diastolic BP	1.00[a]	0.97	1.02	0.75
Night ambulatory systolic BP	1.02[a]	1.00	1.03	0.08
Night ambulatory diastolic BP	1.02[a]	0.99	1.05	0.15
Change between two examinations				
24-h HF (−10 to 10%)	1			0.54
>10%	1.27	0.81	2.00	0.29
⩽−10%	1.33	0.59	2.99	0.49
24-h LF (−10 to 10%)	1			0.08
>10%	1.90	1.03	3.49	0.04
⩽−10%	1.43	0.80	2.53	0.23
24-h VLF (−10 to 10%)	1			0.04
>10%	2.57	1.16	5.70	0.02
⩽−10%	1.55	0.79	3.07	0.21
Day systolic BP (−10 to 10%)	1			0.07
>10%	0.87	0.48	1.58	0.65
⩽−10%	1.79	1.05	3.06	0.03
Day diastolic BP (−10 to 10%)	1			0.001
>10%	0.57	0.19	1.68	0.30
⩽−10%	2.71	1.57	4.65	<0.001
Night systolic BP (−10 to 10%)	1			<0.001
>10%	2.86	1.82	4.48	<0.001
⩽−10%	0.46	0.17	1.21	0.12
Night diastolic BP (−10 to 10%)	1			0.003
>10%	2.38	1.40	4.03	0.001
⩽−10%	0.89	0.48	1.64	0.70
Multivariate model (step-wise logistic regression)				
In 24-h VLF	0.61[a]	0.41	0.91	0.02
Change between two examinations				
Day systolic BP (−10 to 10%)	1			<0.001
>10%	0.32	0.15	0.69	0.004
⩽−10%	3.70	1.79	7.65	<0.001
Day diastolic BP (−10 to 10%)	1			<0.001
>10%	0.61	0.18	2.05	0.61
⩽−10%	3.88	1.96	7.69	<0.001
Night systolic BP (−10 to 10%)	1			<0.001
>10%	7.62	4.19	13.85	<0.001
⩽−10%	0.15	0.05	0.45	0.001

Abbreviations: BP, blood pressure; CI, confidence interval; HF, high frequency; LF, low frequency; OR, odds ratios; VLF, very low frequency.
[a]For 1 s.d. increase.

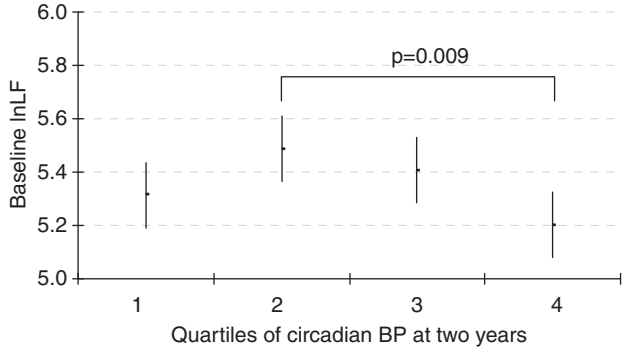

Figure 1 Baseline low frequency according to quartiles of circadian blood pressure 2 years later.

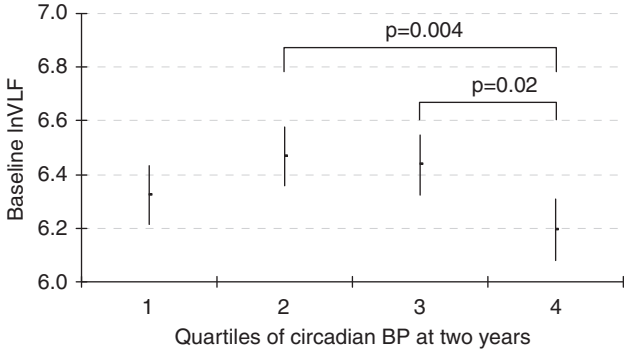

Figure 2 Baseline very low frequency according to quartiles of circadian blood pressure 2 years later.

In our study, we found that lower ANS activity, particularly lower sympathetic tone at baseline, was associated with an increased risk of shift to non-dipper status 2 years later.

The association between a lower VLF at baseline, a sympathetic component of HRV and a higher risk of shift to non-dipper status can be interpreted as an insidious global alteration of the HRV components at baseline because both lower sympathetic and parasympathetic components are related to the onset of impaired variation in circadian BP observed at 2 years of follow-up. The multicollinearity between the HRV indices may explain why the VLF is the persistent significant variable in the multivariate analysis. In addition, the HRV response to parasympathetic tone decreases with age.[20]

Baseline HF tends to be higher, and the LF, VLF and LF/HF ratio tend to be lower, among non-dippers who remain non-dippers in comparison with dippers who remain dippers; nevertheless, the tests do not reach statistical significance. This observation suggests that the non-dipper phenomenon is more deleterious in terms of within-subject autonomic nervous activity changes (variation across time) than between-subject changes (variation at a given time) in this study population. This inference is strengthened by our complementary multivariate analysis performed on the dipper subjects at baseline, which showed the prognostic values of baseline ANS activity indices and their within-subject changes over 2 years with respect to the shift to non-dipper status.

Previous cross-sectional studies have analyzed the relationship between dipper and non-dipper status defined with only one ABPM and ANS activity evaluated through HRV;[6,7] they showed that sympathetic components were lower among non-dipper subjects in different hypertensive populations. Our observations with longitudinal data confirm these results in an untreated population.

In a previous study, VLF was shown to be the component of HRV most associated with sleep-disordered breathing, particularly obstructive sleep apnea syndrome.[21] We do not have data to confirm this hypothesis, but a previous study has shown that sleep-disordered breathing may be involved in the shift to the non-dipper pattern.[22]

Multivariate analysis showed that baseline VLF was associated with the risk of shift to non-dipper status independently of the BP level at baseline and its change between the two examinations. The risk of shift to non-dipper status was related to both day BP decrease and night BP increase between the two examinations. One possible interpretation of this association is that an increase in arterial stiffness, which reduces the sensitivity of baroreceptors, leads to poorer arterial BP adaptation under orthostatic conditions during the entire day (higher BP when lying down and lower BP when standing) and can lead to a shift to non-dipper status. The implication of VLF at baseline and BP change over 2 years in the risk of shift to non-dipper status may be supported by previous studies that have shown a significant relationship between obstructive sleep apneas and an increase in arterial stiffness.[23,24]

Several aspects of our results should be noted. The potential confounding effect of age in the studied relationship was controlled by the design of the PROOF study, in which the subjects had the same age at baseline.[25] Dipper/non-dipper status was defined by systolic BP, which is recognized as a better predictor of morbidity and mortality than diastolic BP.[3,6,7] A study by Boggia *et al.*[26] supports a recommendation that the classification of dipper and non-dipper subjects be conducted with analyses using the continuous variation of arterial BP. In our study, we observed that the relationship between ANS indices and the circadian variation in BP seems to be non-linear. Subjects with insufficient circadian variation in BP had ANS indices that were similar to those of subjects with higher circadian variation. This result is supported by a previous study showing that extreme dipper and non-dipper patterns were associated with silent cerebrovascular damage.[27]

As the introduction of an antihypertensive treatment between the two examinations may have influenced the circadian variation in BP, we verified that withdrawing subjects who started taking such medications did not affect our results. Therefore, we chose to keep them in our analyses to maintain sufficient statistical power.

Our study has several limitations. The findings presented did not include the possible confounding effect of physical activity, which has been shown to have a significant impact on ANS activity indices.[28] The results were adjusted for neither alcohol consumption nor quality of nighttime sleep;[19] however, no difference in the autonomic sleep fragmentation index was observed between dipper and non-dipper status.

The reproducibility of dipper/non-dipper status has been questioned by some authors; it can, therefore, be argued that our study was exposed to classification bias.[18] In addition, the repeated measurements of BP may expose the results to a regression toward the mean. However, we took these limitations into account in the analysis by adjusting the results for the baseline level of BP. We also completed the analysis by studying the quartiles of the circadian variation of BP after 2 years, which reinforced our results.

This study revealed a longitudinal association between impaired ANS activity and a shift to non-dipper status. Impaired ANS activity may alter BP regulation independently of BP level. This suggests that a strategy for treating cardiovascular disease should target, in addition to BP control, the recovery of a normal decrease in nocturnal BP. Further studies should be performed to analyze the potential role of arterial stiffness and sleep-related disorders in the relationship between ANS activity and an insufficient decrease in nocturnal BP.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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