Original Paper

The Relationship Between Nighttime Dipping in Blood Pressure and Cerebral Hemodynamics in Nonstroke Patients

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Inadequate dipping in nighttime blood pressure (BP) is associated with cerebrovascular disease. The authors aimed to determine whether inadequate nocturnal dipping was associated with abnormalities in cerebrovascular hemodynamics in individuals without stroke. Participants in this study underwent 24-hour ambulatory BP monitoring followed by morning transcranial Doppler measurements of blood flow velocities (BFVs) in the middle cerebral artery during supine rest, head-up tilt, hypocapnia, and hypercapnia. Nighttime BP decline by <10% was considered nondipping. Of the 102 nonstroke participants (mean age, 53.6 years), 35 (34%) were dippers. Although nondippers had similar BFV and cerebrovascular resistance (CVR) while supine, they had a lower BFV (P=.04) and greater CVR (P=.02) during head-up tilt compared with dippers. Moreover, greater nighttime dipping in both systolic BP (P=.006) and diastolic BP (P=.03) were associated with higher daytime BFV and lower CVR (P=.01 for systolic BP; P=.02 for diastolic BP). Inadequate nocturnal BP dipping is associated with lower daytime cerebral blood flow, especially during head-up tilt. (J Clin Hypertens. 2007;9:929–936) ©2007 Le Jacq

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Blood pressure (BP) follows a circadian cycle in which it declines during sleep and increases during waking hours.[1] Individuals who do not experience this decline are termed nondippers and are at increased risk for cardiovascular complications and stroke, independent of systemic BP levels.[2–7] Both aging and hypertension are associated with nondipping in BP.[8,9] Recently, nondipping status has been linked to cerebral microvascular disease manifesting as lacunar infarcts, white matter hyperintensities, and cognitive impairment.[6,10–12] Nondipping has also been associated with poor outcome in patients with stroke both acutely and chronically.[13,14] Therefore, nondipping status plays a role in both the onset and the outcomes of cardiovascular and cerebrovascular disease. Ambulatory BP monitoring (ABPM) can assess the circadian changes in BP by measuring BP frequently during the daytime and nighttime. ABPM is better than casual or office BP measurements in predicting cardiovascular disease and end-organ damage from hypertension.[15,16] Moreover, nocturnal dipping in BP is probably the best predictor of vascular outcomes of all BP measures obtained from ABPM.[17]

Developments in transcranial ultrasonographic technology have enabled beat-by-beat evaluations of blood flow velocities (BFVs) in the major cerebral arteries.[18] Continuous measurements of BFV during positional changes such as head-up tilt or biochemical challenges, such as hypercapnia, have allowed investigators to assess cerebrovascular hemodynamics and vasoreactivity noninvasively.[19,20] Two cerebral hemodynamic indices that have been well described in humans include cerebrovascular reactivity to hypercapnia and cerebral autoregulation (or pressure-flow regulation) during

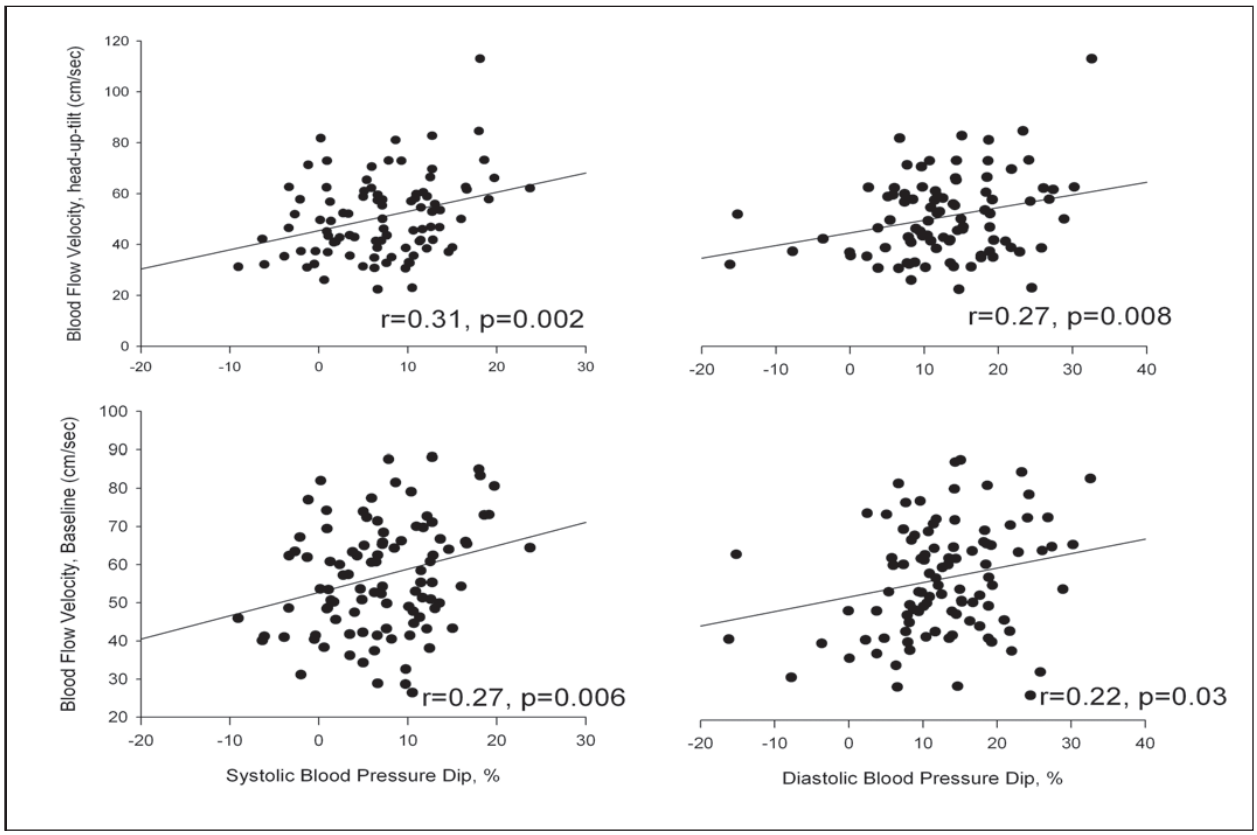

Figure 1. Regression analysis of percent dipping during nighttime systolic and diastolic blood pressure vs mean blood flow velocity during supine rest and head-up tilt.

head-up tilt.[19,21] Abnormalities in cerebral vasoreactivity and in autoregulation have been linked with cerebrovascular disease and stroke.[22,23]

The nature of the association between nondipping in nighttime BP and cerebral blood flow is not known. Prior evidence suggests nondipping at night is associated with abnormal vascular function[24,25] and eventually cerebrovascular damage.[6,12] Abnormal dipping is also associated with increased levels of markers of endothelial dysfunction and inflammation.[25] Both are related to cerebral blood flow and its regulation.[26] Taken together, these data suggest that nondipping may be linked to cerebral blood flow regulation. In fact, a recent study suggests that the degree of nighttime BP decline is associated with increase in regional cerebral blood flow.[5]

Therefore, we hypothesized that individuals with inadequate nighttime dipping in systolic BP (SBP) or diastolic BP (DBP) would demonstrate abnormalities in cerebral blood flow and its regulation during the daytime. Our objective was to assess the association between nighttime dipping in BP with daytime cerebrovascular hemodynamic indices in individuals without clinical history of stroke.

METHODS

Patients

One-hundred sixty participants were recruited from the community via advertisement of the study. Initial recruitment was carried out at the Autonomic Nervous System Laboratory in the Department of Neurology at the Ohio State University (OSU). Patients recruited during the latter part of the study were recruited through the Syncope and Falls in the Elderly laboratory at the Beth Israel Deaconess Medical Center (BIDMC) at Harvard Medical School because of relocation of the investigator from OSU to BIDMC. The devices, sonographer, study protocol, and data acquisition system were identical.

All patients were carefully screened with a medical history and physical and laboratory examinations. This analysis was conducted using data from participants who had no clinical evidence of stroke and had available 24-hour ABPM and BFV data. Participants were excluded if they had a clinical history of stroke and a documented infarct on magnetic resonance imaging (MRI) or computed tomographic (CT) scans. We excluded those with stroke because it affects cerebrovascular hemodynamics acutely and chronically.[27–29] In addition,

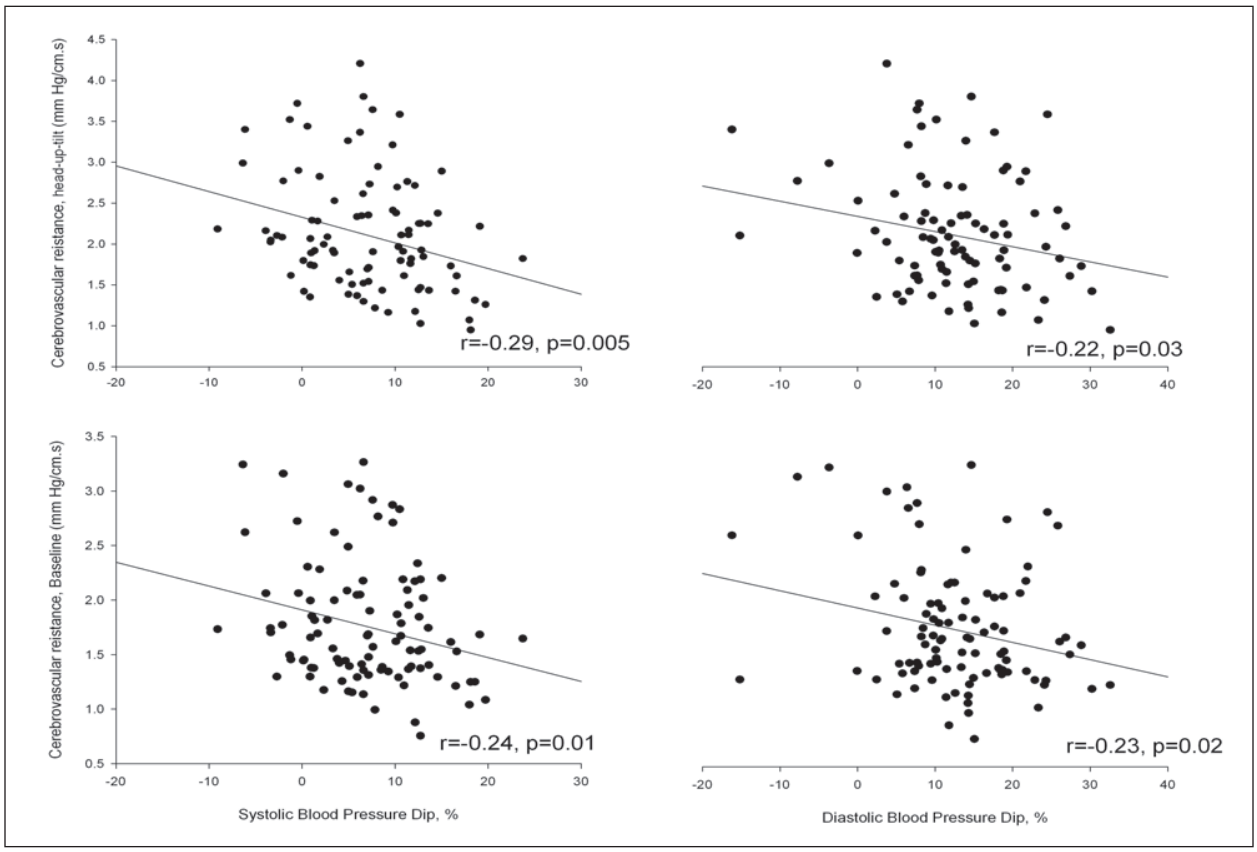

Figure 2. Regression analysis of percent dipping during nighttime systolic and diastolic blood pressure vs mean cerebrovascular resistance during supine rest and head-up tilt.

participants with hemorrhagic strokes, clinically significant cardiac disease and arrhythmias, diabetes, and any other significant systemic illness were also excluded. Individuals with treated hypertension were included. Because of the effect of antihypertensives on hemodynamic measurements, however, these medications were gradually tapered over 3 days; they were discontinued for only 2 days before the study because of safety and ethical reasons. Anticoagulation medications, antihyperlipidemics, and other medications that did not affect cardiovascular or autonomic nervous systems were allowed. If a participant was receiving antihypertensive medication before enrolling in the study, then he or she was considered hypertensive. If the participant was not receiving antihypertensives, he or she was considered hypertensive if mean ABPM was ≥130/80 mm Hg.[30,31] All patients provided written informed consent to an institutional review board–approved protocol.

Data Acquisition, Processing, and Analyses

ABPM was recorded 1 day before performing the transcranial Doppler (TCD) procedure. ABPM was performed with a portable automatic monitor Dynapulse (calibrated by Pulse Metric Inc, Vista, CA) over a 24-hour period from 9 AM to 9 AM following 2 days of no antihypertensive therapy. This monitor has been previously validated against intra-arterial BP measurement with a correlation of 98% ($P<.001$).[32] SBP, DBP, and heart rate were measured at 20-minute intervals during the day and at 30-minute intervals during the night. Patients were asked to lie down at 10 PM and get up at 7 AM. They were asked to avoid exercise other than usual daily activities, which were to be documented in a diary. Data from the portable monitor were then downloaded into a personal computer for analysis. BP was averaged over the 24-hour period (overall SBP and DBP), the daytime (daytime SBP and DBP), and the nighttime (nighttime SBP and DBP). Dipping was calculated according to the standard formula: (daytime BP – nighttime BP) / daytime BP for SBP and DBP.[30,33–35] Using the standard recommendations, a participant was considered a dipper if the drop in SBP or DBP was ≥10% and a nondipper otherwise.[30,33–35]

TCD studies were conducted in the morning after completing the ABPM at 9 AM. Participants were instrumented with 3-lead electrocardiography,

Table I. Demographics and Ambulatory Blood Pressure in the Overall Sample, Dippers, and Nondippers

	Overall (N=102)	Nondippers (n=67)	Dippers (n=35)	*P* Value[a]
Age, y	53.6±1.3	53.8±1.7	53.4±2.0	.94
Female sex	56 (55)	34 (51)	22 (63)	.24
African American race	19 (19)	16 (24)	3 (9)	.07
Body mass index, kg/m^2	28.3±0.7	28.8±0.8	27.2±1.0	.24
Hypertension	48 (47)	32 (48)	16 (46)	.84
Use of antihypertensives	39 (38)	28 (42)	11 (31)	.30
Overall mean				
SBP, mm Hg	130.3±1.5	132.2±2.0	126.8±2.2	.09
DBP, mm Hg	70.6±0.9	71.6±1.2	68.5±1.4	.13
Heart rate, beats per minute	71.4±0.9	70.6±1.1	72.9±1.6	.21
Daytime mean				
SBP, mm Hg	133.2±1.5	133.6±2.0	132.5±2.2	.72
DBP, mm Hg	73.5±1.0	73.8±1.3	73.0±1.5	.70
Heart rate, beats per minute	73.4±1.0	72.5±1.1	75.2±1.7	.18
Nighttime mean				
SBP, mm Hg	123.8±1.6	128.9±2.0	114.2±1.9	<.0001
DBP, mm Hg	64.2±1.0	66.9±1.2	58.8±1.3	<.0001
Heart rate, beats per minute	67.0±0.9	66.4±1.1	68.0±1.66	.44

Data are presented as means ± SE for continuous variables or No. (%). Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. [a]Obtained from the *t* or chi-square tests.

a cuff placed on the finger for beat-to-beat arterial pressure measurement (Finapres device; Ohmeda Monitoring Systems, Englewood, CO), ultrasonographic probes (MultiDop X4; Neuroscan, Inc, Sterling, VA) to measure BFV in the middle cerebral artery (MCA), and an infrared end-tidal volume gas monitor (Capnomac Ultima; Datex-Ohmeda Inc, Louisville, KY) attached to a face mask to measure end-tidal carbon dioxide (CO_2) and oxygen values. All TCD procedures were performed and interpreted by the same experienced sonographer (VN) using the MultiDop X4 TCD machine.

The right and left MCAs were insonated using 2-MHz probes from the temporal windows. Each probe was positioned to record the maximal BFV and stabilized using a 3-dimensional positioning system. Systolic, diastolic, and mean BFVs were detected from the envelope of the arterial flow waveforms. There was no difference between the left and right MCA measurements (pairwise comparison, *P*=.72) in the study population. We used the right MCA data for this analysis.

For the CO_2 reactivity protocol, the patients were asked to breathe a mixture of 5% CO_2 and 95% air from a rebreather bag to increase CO_2 above baseline to 45 mm Hg for 3 minutes, followed by a 5-minute rest to equilibrate CO_2 (CO_2 rebreathing), while continuously measuring BFV. For the head-up tilt, the patient rested in a supine position and then the table was tilted to 70° for 10 minutes. BP, BFV, cerebrovascular resistance (CVR), and pulsatility index were measured during the supine rest and during head-up tilt.

All data were visually inspected for accuracy of R-wave detection, artifacts, and occasional extrasystoles. In addition to mean BFV, the following hemodynamic measures were obtained: 5-minute mean BFV during supine and head-up tilt; CVR calculated from the arterial pressure divided by BFV in the MCA[36]; pulsatility index as defined by Gosling and colleagues[37]; and CO_2 reactivity index.[19] A 30-second average was also calculated for the BFV, minimum during hyperventilation and maximum during CO_2 rebreathing. Vascular reactivity to CO_2 was calculated as a slope of the linear regression of mean BFV and CO_2 between hyperventilation and CO_2 rebreathing.

Statistical Analyses

We used the *t* test and chi-square test to compare the demographics, body mass index (BMI), and clinical characteristics between dippers and nondippers in the study participants.

To study the association between nighttime dipping in SBP and DBP and the hemodynamic indices, we conducted 2 analyses. In the first, we compared cerebrovascular hemodynamic indices between dippers and nondippers as defined previously. In the second, we investigated the association between the degree of nocturnal dipping

Table II. Hemodynamic Indices in Dippers and Nondippers

Nocturnal Dipping	Nondippers (n=67)	Dippers (n=35)	*P* Value[a]
Mean blood pressure,[b] mm Hg			
Supine	94.5±1.8	91.3±2.4	.30
Tilt	99.2±2.2	96.1±2.6	.40
Blood flow velocity, cm/s			
Supine	55.4±1.7	60.2±2.5	.11
Tilt	48.4±1.8	55.2±2.9	.04
Heart rate, beats per minute			
Supine	68.5±1.2	66.2±1.7	.26
Tilt	77.8±1.5	77.2±2.0	.81
Cerebrovascular resistance, mm Hg/cm/s			
Supine	1.8±0.1	1.6±0.1	.06
Tilt	2.2±0.1	1.9±0.1	.02
Pulsatility index			
Supine	0.73±0.02	0.74±0.03	.89
Tilt	0.74±0.03	0.71±0.03	.50
Carbon dioxide reactivity	1.29±0.16	1.34±0.13	.83

[a]Obtained from the *t* test. [b]Averaged beat-to-beat blood pressure during transcranial Doppler procedure.

in SBP and DBP, as a continuous variable, and the hemodynamic indices using regression analyses.

Finally, we performed multivariate analysis using multiple regression analyses to assess the independent association between BP dipping and cerebral hemodynamics, controlling for potential confounders. For each hemodynamic index, a stepwise multivariate model was created because of intercorrelations between variables that included age, sex, race, BMI, use of antihypertensives, and mean arterial pressure (MAP) measured during the TCD procedure. The best-fit model was selected using the overall model *F* statistic.[38] We present the results for the final best-fit model. All analyses were performed using SAS software package (SAS Institute, Cary, NC).

RESULTS

Of the 160 individuals, 39 had evidence of clinical stroke confirmed by CT or MRI, and 19 participants did not have insonation windows to complete the TCD measurements or did not complete the ABPM procedure and were excluded. This analysis was conducted on the 102 nonstroke participants with available TCD and ABPM data.

Table I describes the basic clinical characteristics of the selected sample. Of the 102 participants, 46 (45%) were hypertensive based on the clinical criteria. Thirty-nine (38%) participants were treated for hypertension with 1 or more medications before enrollment: 16 (41%) were on diuretics, 8 (21%) on β-blockers, 9 (23%) on calcium channel blockers, 18 (46%) on angiotensin-converting enzyme inhibitors, and 3 (8%) on angiotensin receptor blockers. These medications were tapered and stopped before performing the study procedures.

Of the 102 participants, 35 (34%) were dippers and 67 (66%) were nondippers. There was no significant difference in the number of dippers between those with and those without hypertension; 14 (30%) of the 46 hypertensives were dippers and 21 (38%) of the 56 normotensives were dippers (*P*=.45). Table I provides the characteristics of the dippers and nondippers in the selected sample. Demographic characteristics, hypertension, and prestudy use of antihypertensive medications were not different between dippers and nondippers. There was a tendency for a higher percentage of African Americans among nondippers. The overall and daytime mean SBP, DBP, and heart rate were similar in both groups, whereas nighttime SBP and DBP were higher in the nondippers (Table I).

Although nondippers had similar BFV and CVR while supine, they had a lower BFV (*P*=.04) and a greater CVR (*P*=.02) during head-up tilt compared with dippers. This was true despite similar BP in both groups during the supine (*P*=.3) and head-up tilt (*P*=.4) positions (Table II). In the multivariate models after adjusting for demographics, BMI, hypertension treatment or diagnosis, and MAP, dippers still demonstrated higher BFV and lower CVR during tilt compared with nondippers. The BFV difference between the 2 groups was 7.3±3.3 cm/s (*P*=.03; model fit [F]=2.3). The CVR difference was 0.3±0.1 mm Hg/cm/s (*P*=.04, model fit [F]=4.2). There was no difference in pulsatility index or CO_2 reactivity between the 2 groups.

When we investigated dipping as a continuous measure, greater nighttime decline in both SBP and DBP was associated with a higher daytime supine BFV (*P*=.006 for SBP dipping; *P*=.03 for DBP dipping) and lower supine CVR (*P*=.01 for SBP dipping; *P*=.02 for DBP dipping). This was also true for head-up tilt BFV and head-up tilt CVR. Figure 1 and Figure 2 present the regression plots for these analyses. In the multivariate analysis after adjusting for age, sex, race, BMI, antihypertensive use, and MAP obtained during TCD procedures, greater SBP and DBP dipping was associated with higher supine BFV (*P*=.007 for SBP dipping; *P*=.003 for DBP dipping) and lower supine CVR (*P*=.02 for SBP dipping; *P*=.02 for DBP dipping). This was also true for the head-up tilt BFV (*P*<.05) and CVR (*P*<.05). These results remained significant after adjusting for the use of antihypertensive medications.

Greater decline in SBP and DBP during the night was also associated with improved CO_2 reactivity, but this association did not reach statistical significance (*r*=0.1, *P*=.38 for SBP; *r*=0.05, *P*=.65 for DBP).

DISCUSSION

The main findings in this study were that greater nocturnal declines in SBP or DBP were associated with a higher daytime BFV and lower CVR, and individuals with nighttime decline in BP <10% (nondippers) demonstrated lower BFV and higher CVR during head-up tilt despite similar supine BFV and CVR. These findings were independent of the presence of hypertension and of receiving antihypertensive medications.

Individuals without adequate nighttime decline in BP are at an increased risk for developing stroke, white matter hyperintensities on MRI, lacunar infarcts, and cognitive impairment.[12,39–43] Our study suggests that nondippers also have greater CVR and lower BFV, especially in the head-up tilt position. This may affect cerebral perfusion during morning activities when individuals assume the upright position. This potentially sheds more light onto the relation between nighttime BP decline and its effect on cerebral hemodynamics. Further, numerous epidemiologic studies have established that there is a disproportionally high frequency of adverse cardiovascular and cerebrovascular events in the morning.[6,40,44] In this study, we identified an association between inadequate degree of dipping in nighttime BP and lower BFV during head-up tilt. Further studies are needed to investigate whether this provides additional explanation for the increase risk of developing stroke and hypoperfusion symptoms in the morning.

The effect of restoring this nocturnal dip, by lowering nighttime SBP, on preventing cerebrovascular events and cognitive impairment warrants further investigation. In addition, comparing the association between diurnal BP changes and cerebral circulatory function in individuals with and without prior stroke may offer further understanding of the complex relation between BP regulation, circadian rhythm, and cerebrovascular disease.

The lack of significant association between SBP and DBP measured by ABPM and CO_2 reactivity is in accordance with prior studies.[45] We observed a trend for an improved CO_2 reactivity in dippers. This, however, did not reach statistical significance.

Our finding that the association between dipping in BP and BFV was independent of prior hypertension status and treatment is of great interest, especially because this suggests that the absence of adequate nighttime decline in BP may pose a negative impact above and beyond hypertension on the cerebrovascular system. Further longitudinal studies to explore this observation are needed.

One limitation of this study is the cross-sectional design, which did not allow us to determine the temporal relation between cerebral blood flow abnormalities and nondipping in BP. Another limitation is that we did not measure BFV during various occasions throughout the day to assess BFV diurnal variation. Prior evidence in rats and humans suggests that cerebral blood flow has a circadian rhythm, and it is usually lower during the night.[46–48] It is not clear, however, whether this change is secondary to change in nighttime BP or independent of BP. Our study suggests that lower nighttime BP, relative to the daytime BP, is associated with lower cerebral blood flow in the morning period despite similar morning BP. Finally, the duration of withdrawal of antihypertensives was limited to 2 days. Although this may affect our BP recordings because of potential residual effect beyond the 2 days, we elected not to withdraw treatment for a longer period for ethical and safety reasons. We did, however, adjust for use of antihypertensives in our analyses.

CONCLUSIONS

Inadequate nocturnal BP dipping may be associated with lower daytime cerebral blood flow, especially during head-up tilt. This effect is independent of the diagnosis of hypertension. Further studies to confirm our observation and to test the possible effect of restoring nighttime dipping on the cerebrovascular system are needed. If confirmed in long-term follow-up studies, our findings may

provide an explanation for the reported association between inadequate BP dipping and cerebrovascular disease.

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REFERENCES

1 O'Brien E, Coats A, Owens P, et al. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. *BMJ*. 2000;320(7242):1128–1134.

2 Giles TD. Circadian rhythm of blood pressure and the relation to cardiovascular events. *J Hypertens Suppl*. 2006;24(2):S11–S16.

3 Tsioufis C, Antoniadis D, Stefanadis C, et al. Relationships between new risk factors and circadian blood pressure variation in untreated subjects with essential hypertension. *Am J Hypertens*. 2002;15(7, pt 1):600–604.

4 Lee AC, Rahman S, Hodges JR, et al. Associative and recognition memory for novel objects in dementia: implications for diagnosis. *Eur J Neurosci*. 2003;18(6):1660–1670.

5 Fujiwara N, Osanai T, Baba Y, et al. Nocturnal blood pressure decrease is associated with increased regional cerebral blood flow in patients with a history of ischemic stroke. *J Hypertens*. 2005;23(5):1055–1060.

6 Shimada K, Kario K. Altered circadian rhythm of blood pressure and cerebrovascular damage. *Blood Press Monit*. 1997;2(6):333–338.

7 Cicconetti P, Morelli S, Ottaviani L, et al. Blunted nocturnal fall in blood pressure and left ventricular mass in elderly individuals with recently diagnosed isolated systolic hypertension. *Am J Hypertens*. 2003;16(11, pt 1):900–905.

8 Yasunari K, Maeda K, Watanabe T, et al. Comparative effects of valsartan versus amlodipine on left ventricular mass and reactive oxygen species formation by monocytes in hypertensive patients with left ventricular hypertrophy. *J Am Coll Cardiol*. 2004;43(11):2116–2123.

9 Munakata M, Imai Y, Abe K, et al. Assessment of age-dependent changes in circadian blood pressure rhythm in patients with essential hypertension. *J Hypertens*. 1991;9(5):407–415.

10 van Boxtel MP, Henskens LH, Kroon AA, et al. Ambulatory blood pressure, asymptomatic cerebrovascular damage and cognitive function in essential hypertension. *J Hum Hypertens*. 2006;20(1):5–13.

11 Puisieux F, Monaca P, Deplanque D, et al. Relationship between leuko-araiosis and blood pressure variability in the elderly. *Eur Neurol*. 2001;46(3):115–120.

12 Yamamoto Y, Akiguchi I, Oiwa K, et al. The relationship between 24-hour blood pressure readings, subcortical ischemic lesions and vascular dementia. *Cerebrovasc Dis*. 2005;19(5):302–308.

13 Pandian JD, Wong AA, Lincoln DJ, et al. Circadian blood pressure variation after acute stroke. *J Clin Neurosci*. 2006;13(5):558–562.

14 Zakopoulos N, Spengos K, Tsivgoulis G, et al. Assessment of blood pressure control in hypertensive stroke survivors: an ambulatory blood pressure monitoring study. *Blood Press Monit*. 2006;11(5):235–241.

15 Bjorklund K, Lind L, Zethelius B, et al. Prognostic significance of 24-h ambulatory blood pressure characteristics for cardiovascular morbidity in a population of elderly men. *J Hypertens*. 2004;22(9):1691–1697.

16 Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med*. 2003;348(24):2407–2415.

17 Mallion JM, Baguet JP, Siche JP, et al. Clinical value of ambulatory blood pressure monitoring. *J Hypertens*. 1999;17(5):585–595.

18 Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg*. 1982;57(6):769–774.

19 Cigada M, Marzorati S, Tredici S, et al. Cerebral CO_2 vasoreactivity evaluation by transcranial Doppler ultrasound technique: a standardized methodology. *Intensive Care Med*. 2000;26(6):729–732.

20 Aaslid R, Newell DW, Stooss R, et al. Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. *Stroke*. 1991;22(9):1148–1154.

21 Tiecks FP, Lam AM, Aaslid R, et al. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke*. 1995;26(6):1014–1019.

22 Derdeyn CP, Grubb RL Jr, Powers WJ. Cerebral hemodynamic impairment: methods of measurement and association with stroke risk. *Neurology*. 1999;53(2):251–259.

23 Cupini LM, Diomedi M, Placidi F, et al. Cerebrovascular reactivity and subcortical infarctions. *Arch Neurol*. 2001;58(4):577–581.

24 Jerrard-Dunne P, Mahmud A, Feely J. Circadian blood pressure variation: relationship between dipper status and measures of arterial stiffness. *J Hypertens*. 2007;25(6):1233–1239.

25 von Kanel R, Jain S, Mills PJ, et al. Relation of nocturnal blood pressure dipping to cellular adhesion, inflammation and hemostasis. *J Hypertens*. 2004;22(11):2087–2093.

26 Ainslie PN, Murrell C, Peebles K, et al. Early morning impairment in cerebral autoregulation and cerebrovascular CO_2 reactivity in healthy humans: relation to endothelial function. *Exp Physiol*. 2007;92(4):769–777.

27 Davis SM, Ackerman RH, Correia JA, et al. Cerebral blood flow and cerebrovascular CO2 reactivity in stroke-age normal controls. *Neurology*. 1983;33(4):391–399.

28 Iizuka T, Sakai F, Ide T, et al. Regional cerebral blood flow and cerebrovascular reactivity during chronic stage of stroke-like episodes in MELAS—implication of neurovascular cellular mechanism. *J Neurol Sci*. 2007;257(1–2):126–138.

29 Vorstrup S, Paulson OB, Lassen NA. Cerebral blood flow in acute and chronic ischemic stroke using xenon-133 inhalation tomography. *Acta Neurol Scand*. 1986;74(6):439–451.

30 O'Brien E, Asmar R, Beilin L, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens*. 2003;21(5):821–848.

31 Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension*. 2003;41(6):1178–1179.

32 Brinton TJ, Cotter B, Kailasam MT, et al. Development and validation of a noninvasive method to determine arterial pressure and vascular compliance. *Am J Cardiol*. 1997;80(3):323–330.

33 Statement on ambulatory blood pressure monitoring by the German Hypertension League. Blood pressure measurement section of the Deutsche Liga zur Bekampfung des hohen Blutdruckes e.V. (German Hypertension League). *J Hum Hypertens*. 1995;9(9):777–779.

34 American Society of Hypertension releases guidelines on home and ambulatory blood pressure monitoring. *Am Fam Physician*. 1996;54(4):1390.

35 Myers MG, Haynes RB, Rabkin SW. Canadian Hypertension Society guidelines for ambulatory blood pressure monitoring. *Am J Hypertens*. 1999;12(11, pt 1):1149–1157.

36 Sugimori H, Ibayashi S, Irie K, et al. Cerebral hemodynamics in hypertensive patients compared with normotensive

volunteers. A transcranial Doppler study. *Stroke*. 1994;25(7):1384–1389.
37 Gosling RG, Lo PT, Taylor MG. Interpretation of pulsatility index in feeder arteries to low-impedance vascular beds. *Ultrasound Obstet Gynecol*. 1991;1(3):175–179.
38 Lipsitz SR, Buoncristiani JF. A robust goodness-of-fit test statistic with application to ordinal regression models. *Stat Med*. 1994;13(2):143–152.
39 Murata T, Takahashi T, Omori M, et al. Association of abnormal diurnal blood pressure variation with the development of silent cerebral infarction in patients with late-life-onset depression. *Gen Hosp Psychiatry*. 2003;25(4):298–300.
40 White WB. Cardiovascular risk and therapeutic intervention for the early morning surge in blood pressure and heart rate. *Blood Press Monit*. 2001;6(2):63–72.
41 Kanemaru A, Kanemaru K, Kuwajima I. The effects of short-term blood pressure variability and nighttime blood pressure levels on cognitive function. *Hypertens Res*. 2001;24(1):19–24.
42 Bastos JM, Bertoquini S, Silva JA, et al. Relationship between ambulatory blood pressure monitoring values and future occurrence of ischemic cerebrovascular and coronary events in hypertensive patients. *Rev Port Cardiol*. 2006;25(3):305–316.
43 Matz K, Tatschl C, Sebek K, et al. Dyslipidemia, elevated LDL cholesterol and reduced nocturnal blood pressure dipping denote lacunar strokes occurring during nighttime. *Eur J Neurol*. 2004;11(11):742–748.
44 Gosse P, Schumacher H. Early morning blood pressure surge. *J Clin Hypertens (Greenwich)*. 2006;8(8):584–589.
45 Fujishima S, Ohya Y, Sugimori H, et al. Transcranial doppler sonography and ambulatory blood pressure monitoring in patients with hypertension. *Hypertens Res*. 2001;24(4):345–351.
46 Wauschkuhn CA, Witte K, Gorbey S, et al. Circadian periodicity of cerebral blood flow revealed by laser-Doppler flowmetry in awake rats: relation to blood pressure and activity. *Am J Physiol Heart Circ Physiol*. 2005;289(4):H1662–H1668.
47 Droste DW, Berger W, Schuler E, et al. Middle cerebral artery blood flow velocity in healthy persons during wakefulness and sleep: a transcranial Doppler study. *Sleep*. 1993;16(7):603–609.
48 Madsen PL, Holm S, Vorstrup S, et al. Human regional cerebral blood flow during rapid-eye-movement sleep. *J Cereb Blood Flow Metab*. 1991;11(3):502–507.