OPEN

Blood Pressure Reverse-Dipping is Associated With Early Formation of Carotid Plaque in Senior Hypertensive Patients

Bin Yan, MD, Liyuan Peng, MD, Donggang Han, MD, PhD, Lu Sun, MD, Quan Dong, MD, Pengtao Yang, MD, Fengwei Zheng, MD, HeanYee Ong, MD, Lingfang Zeng, PhD, and Gang Wang, MD, PhD

Abstract: Nocturnal variations in blood pressure (BP) were associated with carotid intima-media thickness. However, the precise relationship between circadian variations of BP and carotid plaques remains unknown. Therefore, the prognostic value of reverse-dipper pattern of BP for carotid plaque was investigated.

In this cross-sectional study, a total of 524 hypertensive patients were recruited and evaluated with ambulatory BP monitoring between April 2012 and June 2013. Carotid plaque was classified into Grade 0 (normal or no observable plaque), Grade 1 (mild stenosis, 1%–24% narrowing), and Grade 2 (moderate stenosis, ≥25% narrowing). Multinomial logistic regression was applied to analyze the relationship between different degrees of carotid plaque and ambulatory BP monitoring results.

Reverse-dipper pattern of BP was more common in older patients, smokers, and those with elevated fasting glucose. The incidences of coronary artery disease, lacunar infarction, and diabetes were also higher among hypertensive with reverse-dipper pattern. Multinomial logistic regression analysis showed that reverse dipper (odds ratio [OR] 2.500; 95% confidence interval [CI] 1.320–4.736; $P = 0.005$), age (OR 1.089; 95% CI 1.067–1.111; $P < 0.001$), smoke (OR 1.625; 95% CI 1.009–2.617; $P = 0.046$), and diabetes (OR 1.759; 95% CI 1.093–2.830; $P = 0.020$) were significantly different between mild carotid plaque and normal. Our results also suggested that mild carotid plaque was closely related to reverse-dipper pattern of BP (2.308; 95% CI 1.223–4.355; $P = 0.010$).

Reverse-dipper pattern of BP may be a risk factor for carotid atherosclerosis and play a crucial role in the early formation of carotid plaque.

Editor: J. Jose Corbalan.
Received: January 5, 2015; revised: January 26, 2015; accepted: February 9, 2015.
From the Department of Emergency Medicine (BY, GW); Department of Cardiology (LP); Department of Ultrasound (DH, LS); Department of Neurosurgery (QD, FZ); Department of Oncology, the Second Affiliated Hospital, Xi'an Jiaotong University Xi'an, China (PY); Division of Cardiology, Khoo Teck Puat Hospital, Singapore (HYO); and Cardiovascular division, King's College London, British Heart Foundation Centre, London, United Kingdom (LZ).
Correspondence: Dr. Gang Wang, Department of Emergency Medicine, the Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China (e-mail: gang_wang@mail.xjtu.edu.cn).
This work was supported by National Natural Science Foundation of China (No. 81300116), Research Fund of Young Scholars for the Doctoral Program of Higher Education of China (No. 20120201120083), and the Fundamental Research Funds for the Central Universities (No. XJJ2013062).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000604

(*Medicine* 94(10):e604)

Abbreviations: ABPM = ambulatory blood pressure monitoring, BP = blood pressure, CI = confidence interval, CIMT = carotid intima-media thickness, DBP = diastolic blood pressure, OR = odds ratio, SBP = systolic blood pressure.

INTRODUCTION

Hypertension is a well-recognized major risk factor for cardiovascular events. In addition to blood pressure (BP) control, a growing amount of attentions have also been focused on BP variations, which are gradually accepted as an important regulator in the progression of end organ damages in hypertensive patients.[1] It has been established that BP presents a reproducible circadian pattern, arise from endogenous neuroendocrine circadian rhythms and other variables due to physical activity, psychological state, and other exogenous stimuli.[2] Ambulatory blood pressure monitoring (ABPM) is a noninvasive examination to evaluate intermittent BP over 24 hours, whereas patients undergo normal daily activities, including sleep.[3] ABPM can provide valuable diagnostic information for patients with fluctuating BP.[3–5] More importantly, ABPM may facilitate in collecting additional prognostic information of circadian BP variation, which bear a more significant predictive role for cerebral hemorrhage, cardiovascular risk, and all-cause mortality.[6–10] For example, the failure of nocturnal BP dipping increases the risk of organ damages in heart, brain, and kidney.[6,11–14]

On the basis of the nocturnal dipping of BP, circadian BP patterns were used to be divided into dipper (10%–20% systolic blood pressure [SBP] fall), extreme dipper (>20% SBP fall), and nondipper (<10% SBP fall) previously, where reverse-dipper BP pattern (average nighttime BP is higher than daytime BP) was recognized as a variant of nondipper.[15–17] Importantly, reverse dipper was recently regarded as an independent predictor for graft outcome and closely associated with cardiovascular injuries in chronic kidney disease.[18,19] For the first time, we have also discovered that reverse dippers were exposed to higher risk for lacunar infarction,[20] which highlight our hypothesis that BP reverse-dipping might correlate with carotid atherosclerosis. Interestingly, Cuspidi et al[21] and Vasunta et al[22] have reported the association of circadian profile of BP with carotid intima-media thickness (CIMT), which was assessed by B-mode ultrasound of carotid arteries and widely used to evaluate the risk and prognosis of cardiovascular diseases. Therefore, we conducted this cross-sectional study in the patients with hypertension to demonstrate the relationship between the circadian variations of BP and the development of carotid atherosclerosis and provide more prognostic information for cardiovascular events.

METHODS

Study Population

In this study, hypertension was diagnosed as SBP ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg in casual office recording, or daytime (or awake) SBP ≥135 mm Hg and/or DBP ≥85 mm Hg, or night-time (or asleep) SBP ≥120 mm Hg and/or DBP ≥70 mm Hg in ABPM.[23] Data were extracted from our entire in-patient ABPM service database (1740 patients with hypertension) from April 2012 to June 2013. Hypertensive patients were excluded if the patients were <18 or >90 years old; were pregnant female; were under antihypertensive treatment; had BP measurements over 160/100 mm Hg; had night-work employment; had evidences of acute stroke or myocardial infarction within the past 6 months; had sleep apnea syndrome; had evidence of disease or conditions responsible for secondary hypertension; could not tolerate ABPM; had history of any arrhythmia, congestive heart failure, hepatic failure, kidney failure, and significant systemic disease. Five hundred twenty-four hypertensive individuals in total were eventually included in our study. The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital, Xi'an Jiaotong University. All patients were referred because of standard indications that have been shown to use ABPM for appropriate clinical circumstances.

ABPM Assessment

Ambulatory BP was recorded throughout 24 hours using an oscillometric device (Spacelabs 90207; Spacelabs, Redmond, WA). The monitor was installed on the nondominant arm between 7 and 9 AM and removed 24 hours later. Frequency of recordings was made as every 15 minutes during the daytime (from 7 AM to 11 PM) and every 30 minutes during the nighttime (from 11 PM to 7 AM). Strenuous physical activity was discouraged for all patients during the monitoring period. We calculated the following values from the 24-h BP profiles: mean 24-h systolic and diastolic values, SBP- and DBP-awakening, SBP- and DBP-bedtime. The day–night dip in BP was defined for SBP as 10% reduction of the mean BP values at night compared with the daytime values. Values of SBP <70 or >250 mm Hg, DBP <40 or >150 mm Hg, and HR <40 or >150 beats per minute were excluded from the recording. Fewer than 3% of the BP readings were rejected as artifacts on the basis of these criteria. BP patterns of patients in our study were divided into dipper (10%–20% SBP fall), nondipper (0%–10% SBP fall), extreme dipper (>20% SBP fall), and reverse dipper (<0% SBP fall), according to the range of the nocturnal SBP dip.[6,17]

Carotid Artery Measurements

Although the 2010 American College of Cardiology Foundation/American Heart Association guideline for cardiovascular risk assessment recommends (class IIa) the use of CIMT and carotid plaque by ultrasound in asymptomatic adults,[24] the accuracy of CIMT as a marker of atherosclerosis has been questioned with increasingly strong evidence that ultrasound assessment of carotid plaque may have higher predictive power.[25–28] In our study, we mainly focused on the associations between circadian BP variations and the different degrees of carotid plaque. Carotid plaque was measured with duplex ultrasonography with 7.5-MHz linear array transducer. All carotid analyses were performed by 2 individual physicians unaware of the objective and risk factors. The optimal image of carotid artery wall was obtained and the procedure was repeated for 2 times bilaterally. Carotid plaque was examined in diverse segment including proximal common carotid artery (>20 mm proximal to the bulb bifurcation), distal common carotid artery, bulb, internal carotid artery, and external carotid artery on each side and present for any stenosis >0%.[29–31] The degree of carotid artery plaque were divided into Grade 0 (normal or no observable plaque), Grade 1 (mild stenosis, 1%–24% narrowing), and Grade 2 (moderate stenosis, ≥25% narrowing). Because of the lack of patients of severe carotid stenosis (narrowing >70%), we only investigated the relationships between ABPM results and normal, mild stenosis, or moderate stenosis.

Statistical Analysis

Descriptive statistics are presented as percentages for discrete variables and mean ± SD for continuous normally distributed variables. To compare ordinal and continuous normally distributed variables between subgroups of circadian BP and carotid atherosclerosis, chi-squared and analysis of variance were employed, respectively. Variables with statistical significance in univariate models and acceptable collinearity were then included in the multivariate analyses. A multinomial logistic regression was utilized to analyze the relationship between different degrees of carotid atherosclerosis (normal, mild stenosis, and moderate stenosis) and the age, gender, smoking, diabetes, cholesterol, triglycerides, and circadian BP variation. Multinomial logistic regression was also employed to analyze the relationship between circadian BP (dipper, nondipper, and reverse dipper) and different clinical variables. A calculated difference of $P < 0.05$ was considered to be statistically significant. All the data was analyzed using SPSS 18.0 (SPSS Inc, Chicago, IL).

RESULTS

Clinical characteristics of study population with dipping status are shown in Table 1. A total of 524 hypertensive patients including 286 males and 238 females were involved in our study. The male patients tended to have higher 24 hours BP, triglyceride, and blood glucose. The female patients were older, whereas the males were more likely to smoke and had a higher total cholesterol level. However, there was no gender difference in the reverse-dipper pattern of BP (Supplement table 1, http://links.lww.com/MD/A224).

Reverse Dipper Was Correlated With the Progression of Carotid Atherosclerosis

In our study, a total of 111 patients (21.2%) had reverse-dipper BP pattern. Nondipper pattern was observed in 275 hypertensive patients (52.5%) and dipper pattern in 138 patients (26.3%). However, in the absence of data, none of patients in this study had extreme-dipper pattern of BP. Patients of reverse dipper were older and more often smokers, with a higher fasting glucose and glycated hemoglobin (Table 1). There were significantly more patients with coronary artery disease among patients with reverse-dipper pattern.

The distribution of hypertensive patients with different degrees of carotid plaque between each circadian BP pattern group was analyzed using chi-squared test. The difference between dipper and nondipper ($P = 0.037$), dipper and reverse dipper ($P < 0.001$), nondipper, and reverse dipper ($P = 0.009$) were statistically significant. The percentage of moderate carotid stenosis (Grade 2) in the 3 groups with different BP patterns was similar. Patients with reverse-dipper pattern had a

TABLE 1. Characteristics of the Study Population by Dipping Status

Variable	Dipper	Nondipper	Reverse Dipper	*P* Value
Patients, n	138	275	111	
Age, y	58.2 ± 12.7	61.5 ± 12.5*	66.4 ± 11.0* †	0.001
Male/female, n	75/63	156/119	55/56	0.44
Never smoked, n, %	97 (70.3)	140 (50.9)	66 (59.5)	–
Current smokers, n, %	41 (29.7)	135 (49.1)	45 (40.5)	0.001
Coronary artery disease, n, %	44 (31.9)	108 (39.3)	58 (52.3)	0.005
Lacunar infarction, n, %	46 (33.3)	99 (36.0)	50 (45.0)	0.14
Massive cerebral infarction, n, %	6 (4.3)	13 (4.7)	4 (3.6)	0.89
Diabetes, n, %	31 (22.5)	76 (27.6)	38 (34.2)	0.14
Fasting glucose, mmol/L	5.3 ± 2.0	5.3 ± 1.6	5.8 ± 2.6	0.17
Glycated hemoglobin, %	6.5 ± 1.3	6.6 ± 1.4	6.9 ± 1.8	0.41
Triglycerides, mmol/L	2.3 ± 2.1	1.8 ± 1.3*	1.6 ± 1.0*	0.002
Total cholesterol, mmol/L	4.8 ± 1.0	4.6 ± 1.0*	4.6 ± 1.1	0.08
HDL-C, mmol/L	1.2 ± 0.3	1.3 ± 0.5	1.3 ± 0.3	0.49
LDL-C, mmol/L	2.9 ± 1.1	2.7 ± 0.8*	2.7 ± 0.9	0.049
VLD-C, mmol/L	0.7 ± 0.6	0.7 ± 0.6	0.6 ± 0.5	0.29
24 h-SBP, ABPM, mm Hg	132.2 ± 13.0	136.0 ± 14.0*	134.7 ± 13.7	0.032
SBP awakening, mm Hg	136.1 ± 13.6	137.5 ± 14.2	133.8 ± 13.5†	0.063
SBP bedtime, mm Hg	116.5 ± 14.8	130.2 ± 14.0*	139.7 ± 14.4* †	0.001
24 h-DBP, ABPM, mm Hg	78.1 ± 12.1	79.5 ± 10.2	77.5 ± 9.1	0.17
DBP-awakening, mm Hg	81.4 ± 10.8	80.5 ± 10.2	77.4 ± 9.1* †	0.006
DBP-bedtime, mm Hg	68.4 ± 9.9	74.5 ± 9.9*	78.1 ± 10.0* †	0.001

P for difference between the 3 groups. ABPM = ambulatory blood pressure monitoring, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, VLD-C = very low-density lipoprotein cholesterol.

* Indicated control with dipper group $P < 0.05$.

† Indicated control with nondipper group $P < 0.05$.

lowest incidence of Grade 0 carotid artery, whereas had a highest prevalence of mild carotid stenosis (Grade 1) (Figure 1). Therefore, in order to evaluate the influence of different circadian BP pattern, risk factors on the progression of carotid plaque, multinomial regression analyses were performed. It was discovered that reverse dipper (OR 2.500, $P = 0.005$), age (OR 1.089, $P < 0.001$), smoking (OR 1.625, $P = 0.046$), and diabetes (OR 1.759, $P = 0.020$) are significantly different between Grade 1 carotid stenosis (1%–24% narrowing) and Grade 0 (Table 2). Additionally, reverse dipper, nondipper, diabetes mellitus, triglycerides, and total cholesterol were homogeneous comparing Grade 2 carotid stenosis with Grade 1 and 0. In addition to this, circadian decline rate of SBP was shown to be an independently factor for Grade 1 carotid stenosis (OR 0.945, $P = 0.034$) compared with Grade 0 (data not shown).

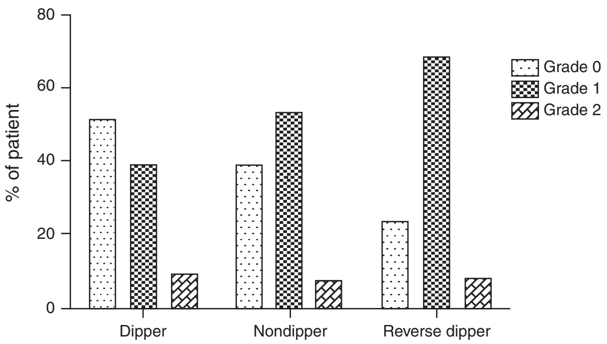

FIGURE 1. The distribution of different degrees of carotid plaque in each circadian BP pattern group. The difference between dipper and nondipper pattern, dipper and reverse-dipper pattern, and nondipper and reverse-dipper pattern were statistically significant ($P = 0.037$, $P < 0.001$, and $P = 0.009$), respectively. Patients with reverse-dipper pattern showed lowest incidence of normal carotid artery and a highest reverse-dipper prevalence of mild stenosis. Grade 0 (normal or no observable plaque), Grade 1 (mild carotid stenosis, 1%–24% narrowing), and Grade 2 (moderate stenosis, ≥25% narrowing).

The Carotid Plaque Affected Circadian Pattern of BP in Hypertensive Patients

Our data indicated that 24-h SBP, SBP-awakening, and SBP-bedtime were elevated in Grade 1 and Grade 2 carotid stenosis (Table 3). The incidences of reverse dipper BP pattern in the Grade 0, 1, and 2 groups were 12.7%, 27.1%, and 23.8%, respectively ($P = 0.007$). Multinomial regression analyses was carried out to investigate further and showed Grade 1 stenosis (OR 2.308, $P = 0.010$), age (OR 1.045, $P < 0.001$), and smoking (OR 2.225, $P = 0.010$) were significantly different between reverse dippers and dippers. However, carotid plaque of all degrees was not significantly different between nondippers and dippers (Table 4).

DISCUSSION

Hypertension is a major risk factor for carotid atherosclerosis, but the fluctuations of BP over a certain period may provide additional prognostic value.[32] For example, visit-to-visit BP variability was considered to be nonspecific but now shown to be associated with stroke, although the degree of

TABLE 2. Comparison of Risk Factor Prevalence Between No Plaque (0% Narrowing), Mild Stenosis (1%–24% Narrowing), and Moderate Stenosis (≥25% Narrowing)

	Mild Stenosis vs No Plaque		Moderate Stenosis vs No Plaque		Moderate Stenosis vs Mild Stenosis		
Variable	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	Global P†
Circadian BP							0.031
Reverse dipper	2.500 (1.320–4.736)	0.005	0.963 (0.316–2.937)	0.95	0.385 (0.136–1.092)	0.073	
Nondipper	1.375 (0.837–2.258)	0.21	0.652 (0.279–1.522)	0.32	0.474 (0.207–1.085)	0.077	
Dipper	1	—	1	—	1	—	
Age, y	1.089 (1.067–1.111)	0.001	1.085 (1.049–1.123)	0.001	0.997 (0.965–1.029)	0.83	<0.001
Gender	0.829 (0.524–1.312)	0.42	0.249 (0.098–0.636)	0.004	0.301 (0.123–0.736)	0.008	0.007
Smoke	1.625 (1.009–2.617)	0.046	3.895 (1.685–9.003)	0.001	2.397 (1.088–5.283)	0.030	0.003
Diabetes	1.759 (1.093–2.830)	0.020	1.457 (0.642–3.306)	0.37	0.828 (0.386–1.778)	0.63	0.062
Triglycerides	1.045 (0.899–1.214)	0.57	0.820 (0.557–1.205)	0.31	0.785 (0.535–1.150)	0.21	0.38
Total cholesterol	0.948 (0.759–1.184)	0.64	0.984 (0.667–1.452)	0.94	1.038 (0.716–1.506)	0.84	0.89

Global P for difference between the 3 groups. BP = blood pressure, CI = confidence interval, OR = odds ratio.

association may be different among studies.[33] Aside long-term BP variability, circadian and minute-to-minute BP variability revealed by ABPM have both been recognized as important cardiovascular risk markers.[34,35] Circadian BP variations were used to be divided into dipper (mean nocturnal BP drops 10 mm Hg or more than that in daytime) and nondipper.[15,16] A previous study showed that nondipper pattern had a tight correlation with increased mean IMT in carotid artery.[22] Interestingly, we found instead of nondipper, nocturnal rise of BP may associate with lacunar infarction in senior hypertensive patients,[20] which alerted the possibility that the pathological role of reverse dipper could be masked by nondipper in population study.

In order to further clarify the impact of different circadian BP pattern in the progression of carotid plaque, we classified the patients as follows: dippers (10%–20% SBP fall), nondippers (0%–10% SBP fall), extreme dippers (>20% SBP fall), and reverse dippers (<0% SBP fall), according to the range of the nocturnal SBP dip.[6,17] As a particular variant of nondipper pattern, reverse-dipper pattern has a higher nighttime BP compared with daytime BP. In addition, based on previous studies, carotid plaque was divided into 3 groups including no plaque (Grade 0, 0% narrowing), mild stenosis (Grade 1, 1%–24% narrowing), and moderate stenosis (Grade 2, ≥25% narrowing).[29,30] Surprisingly, different from other studies on the important prognostic value of nondipper,[17,36,37] our results showed that reverse-dipper pattern of BP is positively associated with the formation of carotid plaque (the initiation of the carotid narrowing <25%) from Grade 0. In consistency with our previous hypothesis, nondipper pattern of BP failed to promote carotid plaque from Grade 0 to Grade 1. Therefore, reverse-dipper pattern of BP showed the strongest independent value to predict carotid plaque formation, not the more severe carotid stenosis. The discovery supports reverse-dipper pattern to be a more accurate tool to evaluate the cardiovascular risks in hypertensive patients in clinics.

Although the associations may exist between reverse-dipper pattern of BP and carotid plaque, the pathophysiological mechanism is incompletely understood. Given the cross-sectional nature of our study, we cannot confirm any direct relationship between reverse dipper and carotid plaque, as they may contribute to each other, or false positively connected by common neuroendocrine factors contributing to both of them. For example, Cuspidi et al[21] found that carotid plaque was an independent predictor of nondipper BP pattern. Interestingly, we also revealed similar results that carotid plaque (mild carotid stenosis) was an independent predictor for reverse-dipper (2.308, 95% CI 1.223–4.355, $P = 0.010$) pattern of BP.

TABLE 3. The Relationship Between BP Parameters and the Development of Carotid Plaque

Variable	No Plaque	Mild Stenosis	Moderate Stenosis	P
Patients, n	205	277	42	
24 h-SBP, ABPM, mm Hg	133.4 ± 13.3	134.8 ± 13.9	138.3 ± 14.3*	0.11
24 h-DBP, ABPM, mm Hg	80.7 ± 11.6	77.1 ± 9.6*	79.0 ± 9.8	0.001
SBP awakening, mm Hg	135.6 ± 13.8	136.2 ± 13.9	139.7 ± 14.7	0.24
DBP awakening, mm Hg	82.4 ± 10.3	78.2 ± 9.8*	80.5 ± 10.0	0.001
SBP bedtime, mm Hg	124.8 ± 16.2	130.4 ± 16.2	132.1 ± 17.0*	0.001
DBP bedtime, mm Hg	74.6 ± 10.8	72.7 ± 10.2	74.2 ± 10.7	0.14
Nighttime BP increase, n, %	26 (12.7)	75 (27.1)	10 (23.8)	0.007

P for difference between the 3 groups. ABPM = ambulatory blood pressure monitoring, DBP = diastolic blood pressure, SBP = systolic blood pressure.

* Indicated control with no plaque group $P < 0.05$. † Indicated control with mild stenosis (1%–24% narrowing) group $P < 0.05$.

TABLE 4. Multinomial Logistic Regression Analysis Between Reverse Dipper, Nondipper, and Dipper

	Reverse Dipper vs Dipper		Nondipper vs Dipper		Reverse Dipper vs Nondipper		
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**Global *P*†**
Carotid plaque						0.069	
Moderate stenosis	1.084 (0.369–3.183)	0.88	0.692 (0.299–1.604)	0.39	1.567 (0.590–4.161)	0.37	
Mild stenosis	2.308 (1.223–4.355)	0.010	1.338 (0.820–2.183)	0.24	1.725 (0.979–3.038)	0.059	
Normal	1	—	1	—	1	—	
Age, y	1.045 (1.020–1.071)	0.001	1.021 (1.001–1.041)	0.039	1.024 (1.002–1.046)	0.030	0.002
Gender	1.467 (0.827–2.602)	0.19	1.211 (0.758–1.935)	0.42	1.211 (0.741–1.980)	0.44	0.42
Smoke	2.225 (1.215–4.074)	0.010	2.751 (1.679–4.508)	0.001	0.809 (0.492–1.329)	0.40	<0.001
Diabetes	1.483 (0.826–2.665)	0.19	1.185 (0.724–1.941)	0.50	1.252 (0.766–2.045)	0.37	0.42

Global *P* for difference between the 3 groups. CI = confidence interval, OR = odds ratio.

To study the mechanism underlying BP variability and carotid atherosclerosis, a few researchers proposed that the higher risk of carotid atherosclerosis associated with nondipper pattern of BP may relate to relatively higher blood mechanical forces on endothelial cells, or elevated levels of molecules related to endothelial dysfunction.[38,39] Additionally, the changes in aortic wall structure and related reduction in aortic dispensability might have been direct consequences of increased BP variability.[40] On the contrary, BP variability depends on the sensitivity of arterial baroreceptor, which could be compromised due to reduced large arterial compliance.[33] However, Sasaki et al[41] and Lacolley et al[42] provided evidence that rats arterial baroreceptor denervation could induce not only abnormal BP variation, but aortic stiffness and atherosclerosis. Therefore, future prospective studies in human are needed to look into the potential network of regulation.[43]

Ultrasound assessment of carotid artery is a straightforward, inexpensive, and noninvasive imaging test to evaluate the cardiovascular risk of patient.[44] Either carotid plaque or CIMT was shown to predict cardiovascular outcomes and ischemic stroke.[45–48] Mathiesen et al[48] suggested that total plaque area and CIMT were closely related to the first-ever ischemic stroke. However, a body of evidence indicated that the carotid plaque represent the stage of atherosclerotic pathogenesis more accurately than CIMT.[27] A published meta-analysis also revealed that the ultrasound detection of carotid plaque had a higher prognostic accuracy for the prediction of future CAD events compared with that of CIMT.[28] These findings may greatly enhance the prognostic value of our discovery in BP dipping status.

To our knowledge, this is the first study to report the association between reverse-dipper pattern of BP and initial formation of carotid plaque in individuals with hypertension. Therefore, the development of antihypertensive medicine with an effect on lowering nocturnal BP may influence the development of carotid plaque. However, our study was launched in the Northern Chinese population of essential hypertension. Therefore, the result should not be extended to nonhypertensive patient and other ethnic groups. Additionally, we only investigated the circadian BP pattern, whereas multiple ABPM over a longer period of time may provide more prognostic information. Further studies are needed to address the impact of extreme-dipper pattern on carotid atherosclerosis in hypertensive patients. Moreover, prospective clinical observation may facilitate better understanding of the underlying mechanism.

ACKNOWLEDGEMENTS

We are grateful to Dr Yuan Shen from the Department of Statistics, Xi'an Jiaotong University School of Medicine, for her advices and supports on searching strategy and statistics. We also acknowledge the support from the patients who participated in our research.

REFERENCES

1. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet.* 2010;375:938–948.
2. Izzedine H, Launay-Vacher V, Deray G. Abnormal blood pressure circadian rhythm: a target organ damage? *Int J Cardiol.* 2006;107:343–349.
3. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. *N Engl J Med.* 2006;354:2368–2374.
4. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension.* 1994;24:793–801.
5. Hansen TW, Li Y, Boggia J, et al. Predictive role of the nighttime blood pressure. *Hypertension.* 2011;57:3–10.
6. Kario K, Pickering TG, Matsuo T, et al. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension.* 2001;38:852–857.
7. Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA.* 1999;282:539–546.
8. Metoki H, Ohkubo T, Kikuya M, et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. *Hypertension.* 2006;47:149–154.
9. 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;348:2407–2415.
10. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation.* 2005;111:1777–1783.
11. Cuspidi C, Macca G, Sampieri L, et al. Target organ damage and non-dipping pattern defined by two sessions of ambulatory blood pressure monitoring in recently diagnosed essential hypertensive patients. *J Hypertens.* 2001;19:1539–1545.

12. 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;16:900–905.
13. Cuspidi C, Meani S, Salerno M, et al. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. *J Hypertens.* 2004;22:273–280.
14. Bianchi S, Bigazzi R, Baldari G, et al. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. *Am J Hypertens.* 1994;7:23–29.
15. McAlister FA, Straus SE. Evidence based treatment of hypertension. Measurement of blood pressure: an evidence based review. *BMJ.* 2001;322:908–911.
16. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet.* 1988;2:397.
17. Routledge F, McFetridge-Durdle J. Nondipping blood pressure patterns among individuals with essential hypertension: a review of the literature. *Eur J Cardiovasc Nurs.* 2007;6:9–26.
18. Ibernon M, Moreso F, Sarrias X, et al. Reverse dipper pattern of blood pressure at 3 months is associated with inflammation and outcome after renal transplantation. *Nephrol Dial Transplant.* 2012;27:2089–2095.
19. Wang C, Zhang J, Liu X, et al. Reversed dipper blood-pressure pattern is closely related to severe renal and cardiovascular damage in patients with chronic kidney disease. *PLoS One.* 2013;8:e55419.
20. Yan B, Peng L, Dong Q, et al. Reverse-dipper pattern of blood pressure may predict lacunar infarction in patients with essential hypertension. *Eur J Neurol.* 2015. doi: 10.1111/ene.12659.
21. Cuspidi C, Meani S, Lonati L, et al. Short-term reproducibility of a non-dipping pattern in type 2 diabetic hypertensive patients. *J Hypertens.* 2006;24:647–653.
22. Vasunta RL, Kesaniemi YA, Ylitalo A, et al. Nondipping pattern and carotid atherosclerosis in a middle-aged population: OPERA study. *Am J Hypertens.* 2012;25:60–66.
23. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2013;31:1281–1357.
24. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2010;56:e50–e103.
25. Johnsen SH, Mathiesen EB, Joakimsen O, et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons—the Tromso study. *Stroke.* 2007;38:2873–2880.
26. Finn AV, Kolodgie FD, Virmani R. Correlation between carotid intimal/medial thickness and atherosclerosis: a point of view from pathology. *Arterioscler Thromb Vasc Biol.* 2010;30:177–181.
27. Plichart M, Celermajer DS, Zureik M, et al. Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study. *Atherosclerosis.* 2011;219:917–924.
28. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis.* 2012;220:128–133.
29. Wilson PW, Hoeg JM, D'Agostino RB, et al. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med.* 1997;337:516–522.
30. Chien KL, Su TC, Jeng JS, et al. Carotid artery intima-media thickness, carotid plaque and coronary heart disease and stroke in Chinese. *PLoS One.* 2008;3:e3435.
31. Polak JF, Tracy R, Harrington A, et al. Carotid artery plaque and progression of coronary artery calcium: the multi-ethnic study of atherosclerosis. *J Am Soc Echocardiogr.* 2013;26:548–555.
32. Parati G, Ochoa JE, Salvi P, et al. Prognostic value of blood pressure variability and average blood pressure levels in patients with hypertension and diabetes. *Diabetes Care.* 2013;36 (suppl 2): S312–S324.
33. Nagai M, Kario K. Visit-to-visit blood pressure variability, silent cerebral injury, and risk of stroke. *Am J Hypertens.* 2013;26:1369–1376.
34. Fagard RH, Celis H, Thijs L, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension.* 2008;51:55–61.
35. Schillaci G, Parati G. Determinants of blood pressure variability in youth: at the roots of hypertension. *J Hypertens.* 2010;28:660–664.
36. Yokota H, Imai Y, Tsuboko Y, et al. Nocturnal blood pressure pattern affects left ventricular remodeling and late gadolinium enhancement in patients with hypertension and left ventricular hypertrophy. *PLoS One.* 2013;8:e67825.
37. Borel AL, Benhamou PY, Baguet JP, et al. Short sleep duration is associated with a blood pressure nondipping pattern in type 1 diabetes: the DIAPASOM study. *Diabetes Care.* 2009;32:1713–1715.
38. Stolarz K, Staessen JA, O'Brien ET. Night-time blood pressure: dipping into the future? *J Hypertens.* 2002;20:2131–2133.
39. von Kanel R, Jain S, Mills PJ, et al. Relation of nocturnal blood pressure dipping to cellular adhesion, inflammation and hemostasis. *J Hypertens.* 2004;22:2087–2093.
40. Lacolley P, Bezie Y, Girerd X, et al. Aortic distensibility and structural changes in sinoaortic-denervated rats. *Hypertension.* 1995;26:337–340.
41. Sasaki S, Yoneda Y, Fujita H, et al. Association of blood pressure variability with induction of atherosclerosis in cholesterol-fed rats. *Am J Hypertens.* 1994;7:453–459.
42. Lacolley P, Glaser E, Challande P, et al. Structural changes and in situ aortic pressure-diameter relationship in long-term chemical-sympathectomized rats. *Am J Physiol.* 1995;269:H407–H416.
43. Schillaci G, Bilo G, Pucci G, et al. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension.* 2012;60:369–377.
44. Wyman RA, Mays ME, McBride PE, et al. Ultrasound-detected carotid plaque as a predictor of cardiovascular events. *Vasc Med.* 2006;11:123–130.
45. Cao JJ, Arnold AM, Manolio TA, et al. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the Cardiovascular Health Study. *Circulation.* 2007;116:32–38.
46. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation.* 2007;115:459–467.
47. Polak JF, Pencina MJ, Pencina KM, et al. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med.* 2011;365:213–221.
48. Mathiesen EB, Johnsen SH, Wilsgaard T, et al. Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromso study. *Stroke.* 2011;42:972–978.