Circadian Blood Pressure Variations in Postmenopausal Females with Hypertension

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Summary

The abnormalities of blood pressure (BP) nocturnal decline have been found to be predictive for carotid plaque and lacunar infarction in patients with hypertension. In this study, BP dipping patterns in postmenopausal females with hypertension were investigated. The nocturnal decline of systolic BP (SBP) was evaluated using 24-hour ambulatory BP monitoring (ABPM). A total of 163 postmenopausal females were eventually included in our study. The prevalence of reverse-dipper BP pattern was 32.3% in females with menopause age in their 40s and 40% in their 50s. However, after multivariate logistic regression analysis, menopause age was shown to be an independent risk factor for BP reverse dipping (Odds ratio [OR] 1.148; 95%CI 1.020 - 1.292; $P = 0.020$). Moreover, menopause age was negatively correlated with the decline rate of nocturnal SBP ($r = -0.159$; $P < 0.05$) and diastolic BP ($r = -0.161$; $P < 0.05$). Our study suggested that the menopause age might serve as a risk factor for reverse-dipper BP pattern in postmenopausal females with hypertension.

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Key words: Essential hypertension, Circadian BP patterns, Menopause age

Young women are less likely to suffer from cardiovascular disease (CVD) than men, although this advantage is rapidly reversed after menopause, which is considered because of the protective effect of estrogen on the cardiovascular system.¹⁾ CVD rates in women after menopause are 2 - 3 times those of the same age before menopause.²⁾ Furthermore, studies have indicated a higher risk of cardiovascular heart disease (CHD), heart failure (HF), CVD mortality and overall mortality in women who experience premature or early-onset menopause.^{3,4)} The prevalence of hypertension, which is one of the main risk factors for CVD, is known to increase with age,⁵⁾ so proper management of blood pressure (BP) in peri- and postmenopausal women is essential for the prevention of CVD in later life.

Ambulatory blood pressure monitoring (ABPM), which offers us the average BP, variability, and circadian dipping status across a 24-hour (24-h) period, has better reproducibility and prognostic superiority compared with standard clinical measurements.^{6,9)} According to the ratio of systolic blood pressure (SBP) at night and day based on ABPM data, circadian BP variations were used to be divided into dipper (mean nocturnal SBP drops 10 mmHg or more than that in daytime) and non-dipper (all other

subjects). As a particular variant of non-dipper pattern, reverse-dipper defined as an increase in SBP at night, which was found to be associated with higher incidence of cardiovascular events.¹⁰⁾ Consistently, our previous study also suggested that BP reverse dipping was the real risk factor for carotid atherosclerosis, diabetes mellitus (DM) and lacuna infarction.¹¹⁻¹³⁾

We conducted this study to investigate the relationship between menopause age and reverse-dipper BP pattern. Moreover, we tried to evaluate the potential association of menopause age with the decline rate of nocturnal BP in all hypertensive patients.

Methods

Study population: A total of 163 postmenopausal females with essential hypertension were eventually included in our study. All inpatients were recruited from January 2012 to June 2014 in Xi'an, Shaanxi Province, China. Data were extracted from our entire in-patient ABPM service database. Age at menopause was defined as the age at last menstrual period or bilateral oophorectomy. Hypertension patients was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg in casual office record-

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Table I. Characteristics of the Study Population by Dipping Status

Variable	Dippers	Non-dippers	Reverse-dippers	P
Patients, <i>n</i>	18	87	58	
Age, years	64.4 ± 9.6	64.5 ± 10.3	64.6 ± 9.1	0.998
Diabetes, <i>n</i> (%)	3 (16.7)	26 (29.9)	20 (34.5)	0.325
History of smoking, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	---
Menopausal age, years	45.8 ± 6.0	48.1 ± 4.0*	48.6 ± 3.6 [#]	0.054
Triglycerides (mmol/L)	1.9 ± 0.8	1.8 ± 1.0	1.7 ± 1.3	0.728
Total cholesterol (mmol/L)	5.0 ± 0.8	4.7 ± 0.9	4.9 ± 1.1	0.391
HDL-C (mmol/L)	1.3 ± 0.2	1.3 ± 0.3	1.3 ± 0.3	0.405
LDL-C (mmol/L)	3.0 ± 0.7	2.7 ± 0.7	2.9 ± 0.9	0.260
VLD-C (mmol/L)	0.6 ± 0.4	0.7 ± 0.5	0.7 ± 0.6	0.918
24 h-SBP, ABPM (mmHg)	132.1 ± 12.1	133.7 ± 14.2	133.5 ± 15.3	0.911
24 h-DBP, ABPM (mmHg)	75.7 ± 9.2	73.7 ± 8.7	75.9 ± 8.6	0.286
SBP-awakening, (mmHg)	136.2 ± 12.9	134.7 ± 14.2	131.9 ± 14.2	0.384
DBP-awakening, (mmHg)	78.7 ± 9.8	74.2 ± 7.9	75.6 ± 8.2	0.100
SBP-bedtime, (mmHg)	116.6 ± 11.0	128.3 ± 13.8*	137.0 ± 14.5* [#]	0.001
DBP-bedtime, (mmHg)	64.3 ± 8.2	69.8 ± 8.4*	76.2 ± 9.2* [#]	0.001

P for difference among the 3 groups. ABPM indicates ambulatory blood pressure monitoring; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; and VLD-C, very low-density lipoprotein cholesterol. *Control with dipper group, *P* < 0.05, [#]Control with non-dipper group, *P* < 0.05.

ing, or daytime (or awake) SBP ≥ 135 mmHg and/or DBP ≥ 85 mm Hg, or night-time (or asleep) SBP ≥ 120 mm Hg and/or DBP ≥ 70 mmHg in ABPM. DM was defined as a fasting blood glucose level ≥ 7.0 mmol/L, non-fasting blood glucose ≥ 11.1 mmol/L, a self-reported physician diagnosis of DM, or current use of antidiabetic medication. The nocturnal decline of SBP was evaluated using 24-hour ABPM. In this study, the circadian decline rate of SBP fluctuating from 10% to 20% was considered as BP dipping pattern. Non-dipper (0% to 10% SBP fall) and reverse-dipper (SBP nocturnal rise) were also investigated. In addition, no extreme dipper (> 20% nocturnal SBP fall) was observed in this study.

The hypertensive patients were excluded if they 1) were < 30 or > 90 years old; 2) were under antihypertensive treatment; 3) had a BP over 160/100 mmHg; 4) were night workers; 5) had acute stroke or myocardial infarction within the past 6 months; 6) had sleep apnea syndrome; 7) were diagnosed with secondary hypertension; 8) could not tolerate the ABPM; 9) had other chronic diseases.

ABPM assessment: All patients underwent 24-hour ABPM using an oscillometric device (Spacelabs 90207; Spacelabs, Redmond, WA). BP was recorded at every 15 minutes from 7:00AM to 11:00PM (diurnal BP values) and every 30 minutes from 11:00PM to 7:00AM (nocturnal BP values). Subjects were instructed not to exercise before or during the monitoring period and to pause momentarily and maintain their body position during each BP measurement. Monitoring was done on a working day. Patients were asked to attend their usual activities but to keep motionless at the time of measurement. Only recordings of good technical quality (> 70% of valid BP measurements) were included in final analyses.⁸⁾ All ABPM recordings were manually edited by two individual physicians unaware of the objective and risk factors. Values of SBP < 70 or > 250 mmHg, DBP < 40 or > 150 mmHg,

and heart rate < 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. The percent change in nocturnal blood pressure decline was calculated as follows: (mean diurnal BP - mean nocturnal BP)/mean diurnal BP × 100.

Laboratory tests: Baseline demographic, clinical and laboratory data were carefully recorded. Peripheral blood samples were drawn routinely from patients in a fasting state. Plasma concentrations of glucose, lipids and other biochemical parameters were determined at the Biochemistry Department in our hospital.

Statistical analysis: Descriptive statistics are presented as percentages for discrete variables and mean ± SD for continuous normally distributed variables. An ANOVA test was used for statistical comparison of data that were normal distributed. The distribution of three circadian BP patterns among postmenopausal females with different menopause age was analyzed using a chi-squared test. Multivariate logistic regression analyses were applied to explore the relationship between the relevant variable and ABPM result. Bivariate correlation analysis was employed to examine the association between menopause age and the decline rate of nocturnal BP. *P*-values < 0.05 were considered statistically significant for all analyses. All statistical analyses were performed using the SPSS software package version 18.0 (SPSS Inc., Chicago, IL, USA).

The study protocol was approved by the ethics committee of the Second Affiliated Hospital, Xi'an Jiaotong University. All subjects consented to participate after been informed of the nature and purpose of the study.

Results

Clinical and laboratory characteristics of the study population: The demographic and clinical characteristics of patients in different groups according to circadian vari-

Figure 1. The distribution of three circadian BP patterns among postmenopausal females with different menopause age.

Table II. Univariate and Multivariate Logistic Regression Analysis for Circadian BP Pattern

Variable	Reversed-dipper versus Dipper		Non-dipper versus dipper		Reversed-dipper versus Non-dipper	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	0.985 (0.930-1.044)	0.619	0.986 (0.933-1.043)	0.628	0.999 (0.963-1.036)	0.954
Diabetes	2.775 (0.674-11.435)	0.158	2.209 (0.577-8.757)	0.259	1.256 (0.602-2.621)	0.543
Triglycerides	0.799 (0.457-1.396)	0.430	0.983 (0.591-1.635)	0.947	0.813 (0.559-1.181)	0.277
Total cholesterol	1.024 (0.554-1.893)	0.94	0.779 (0.430-1.411)	0.410	1.315 (0.911-1.899)	0.140
Menopausal age	1.148 (1.020-1.292)	0.02	1.113 (1.000-1.239)	0.050	1.031 (0.943-1.127)	0.497

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

ations of BP were shown in Table I. A total of 163 hypertensive patients, including 18 dippers (11.0%), 87 non-dippers (53.4%) and 58 reverse-dippers (35.6%), were involved in our study. There were no significant differences in age, diabetes, history of smoking, triglycerides, and cholesterol among the three groups. In addition, there was a significant difference ($P = 0.016$) in menopause age between reverse dippers (48.6 ± 3.6) and dippers (45.8 ± 6.0).

Association of menopause age with circadian BP patterns: The distribution of three circadian BP patterns (dipper, non-dipper, reverse-dipper) among postmenopausal females with different menopause age was analyzed using a chi-squared test. As shown in Figure 1, the prevalence of reverse-dipper BP pattern was 32.3% in females with menopause age of 40s and 40% at 50s.

Furthermore, a univariate multinomial logistic regression analysis using stepwise selection process was performed in our study. Our univariate models included age, diabetes, smoking, menopause age, triglycerides, HDL-C, LDL-C, VLD-C, 24h-SBP, 24h-DBP, SBP-awakening, SBP-bedtime, DBP-awakening and DBP-bedtime. The variables found to have significance and acceptable collinearity in univariate models were included in the multinomial analyses. It was discovered that menopause age was significantly different when comparing reverse-dipper BP pattern with dipper pattern (Table II). This model suggested that menopause age was an independent risk factor for BP reverse dipping with essential hypertension (Odds ratio [OR] 1.148; 95% CI 1.020 - 1.292; $P = 0.020$).

Correlation between menopause age and decline rate of nocturnal BP: Nocturnal BP has been considered to be

a more important risk factor than office BP since it is not affected by the “white coat effect.”^{14,15} A decrease of 10%-20% in night-time BP has been considered to be a normal level of dipping. Lack of nocturnal reduction that is less than 10% compared to the day time BP value has been associated with increased CVD risk factors.¹⁶ In order to further clarify the relationship between menopause age and the decline of nocturnal BP, bivariate correlation analysis was performed. Consistently, we found that menopause age was negatively correlated with the decline rate of nocturnal SBP ($r = -0.159$; $P < 0.05$) and DBP ($r = -0.161$; $P < 0.05$) (Figure 2).

Discussion

BP has a circadian rhythm in which it decreases at night and increases in the morning; nocturnal dipping of blood pressure is an important physiologic phenomenon. Absence of the normal nocturnal fall in SBP is associated with increased morbidity and mortality, and poses a substantial risk even after antihypertensive treatment.¹⁷⁻¹⁹ Studies have reported the association of non-dipper pattern of BP with carotid intima-media thickness (CIMT), which was assessed by B-mode ultrasound and widely performed to evaluate the risk and prognosis of cardiovascular diseases.^{20,21} Patients with a non-dipper pattern have more target-organ damage induced by hypertension, such as left ventricular hypertrophy, microalbuminuria, and reduced arterial compliance. Reverse-dipper hypertension, which was categorized as a variant of non-dipper, was recently regarded as an independent predictor for graft outcome and closely associated with cardiovascular injuries in chronic kidney disease.^{22,23} In addition, reverse-dipper

Figure 2. **A:** The relationship of menopause age and decline rate of nocturnal SBP. **B:** The relationship of menopause age and decline rate of nocturnal DBP.

was found to be predictor of cardiovascular events in hypertensive patients.²⁴⁾ We have also previously found that reverse-dipper pattern of BP was significantly associated with the type 2 diabetes, carotid atherosclerosis and lacuna infarction.¹¹⁻¹³⁾ Hence, restoration of the physiological

circadian rhythm may be an aspect of crucial importance in the treatment of hypertensive patients independent of normalization of elevated BP values.²⁵⁾

Menopause is the permanent cessation of menstruation, which is characterized by physiological changes that

influence several organs and systems. The lower estrogen level of postmenopausal women is generally regarded as the main reason for an increased risk of cardiovascular diseases.⁴⁾ Studies have shown that women are at a lesser risk of developing cardiovascular disease than their male counterparts before menopause, but this advantage is abolished after menopause.²⁶⁻²⁸⁾ Additionally, the Framingham Study suggested that female CHD morbidity rates accelerate more quickly than do those of males after the age of 45 years.²⁹⁾ So, identification of women with early menopause offers a window of opportunity to implement interventions that will improve overall cardiovascular health during the postmenopausal years.

Despite the extensive research on the relationship of menopause age and cardiovascular disease, it is not yet clear whether menopause age associated with circadian variations of BP, in which reverse-dipper has been demonstrated as a risk of CHD in essential hypertension patients in our previous study (unpublished data). To our knowledge, this is the first study to report the relationship between menopause age and circadian blood pressure variations. We found that menopause age of reverse-dipper BP pattern was significantly later than dipper pattern. Furthermore, the menopause age was negatively correlated with the decline rate of nocturnal SBP and DBP. Our study suggested that the menopause age might serve as an independent risk factor for reverse-dipper BP pattern in postmenopausal females with hypertension. The possible mechanism of the relationship between menopause age and circadian variations of BP is proposed to be estrogen's deficiency inducing endothelial dysfunction, dyslipidemia and increased body mass index in postmenopausal.³⁰⁾ However, the detailed mechanism remains to be further investigated.

Study limitations: Several potential limitations of our study should be noted. First, our study had a cross-sectional design; it is possible that the results might be affected by the difference of duration between the time of 24-hour ABPM and the time of menopause among each group of circadian blood pressure, whereas a longer period of prospective observation may provide more prognostic information. Secondly, it will be more powerful if a larger sample size is employed. Thirdly, the reproducibility of ABPM is controversial because of the large influence of daily activity on BP.³¹⁾ Finally, the patients in our study are exclusively limited to northern Chinese patients from a single center, so the results should not be extended to different ethnic groups. Therefore, further prospective clinical observation with more rigorous design is necessary.

Disclosures

Conflicts of interest: The authors have no conflicts of interest regarding the content of the manuscript.

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