Associations of dipping and non-dipping hypertension with cardiovascular diseases in patients with dyslipidemia

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Submitted: 8 October 2017
Accepted: 11 December 2017

Arch Med Sci 2019; 15, 2: 337–342
DOI: https://doi.org/10.5114/aoms.2018.72609

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Abstract

Introduction: Dyslipidemia combined with hypertension increases the risk of cardiovascular disease (CVD). The current study aimed to investigate the association of dipping and non-dipping hypertension with CVD in patients with dyslipidemia.

Material and methods: A total of 243 documented dyslipidemia patients with hypertension were enrolled. Clinical characteristics and clinic and 24-hour blood pressure (BP) parameters were compared between dipping and non-dipping groups based on 24-hour ambulatory blood pressure monitoring. Logistic regression analysis was performed to evaluate the association of dipping and non-dipping hypertension with CVD.

Results: Compared to the dipping group, patients in the non-dipping group were older, more likely to be male and smokers, had higher serum creatinine levels, and were more likely to have chronic kidney disease and CVD ($p < 0.05$ for all comparisons). No significant between-group differences in clinic systolic and diastolic BP (SBP and DBP) were observed. However, compared to the dipping group, 24-hour SBP, nighttime SBP and DBP, and night-day ratio of SBP and DBP were all significantly higher in the non-dipping group ($p < 0.05$ for all comparisons). In the dipping group, only night-day ratio of SBP was significantly associated with CVD, with an odds ratio (OR) of 1.09 (95% confidence interval (CI) of 1.02–1.34). In the non-dipping group, both night-day ratio of SBP and DBP were significantly associated with CVD, with an OR of 1.72 (95% CI: 1.33–2.06) and 1.23 (95% CI: 1.05–1.66), respectively.

Conclusions: In patients with dyslipidemia, non-dipping hypertension is more closely related to CVD compared to dipping hypertension.

Key words: dyslipidemia, hypertension, cardiovascular diseases.

Introduction

Cardiovascular diseases (CVD) are a leading cause of morbidity and mortality around the world [1, 2]. Among the risk factors of CVD, dyslipidemia and hypertension are the most important ones [3–5]. It is reported that dyslipidemia combined with hypertension accounted for more than half of population attributable risks of CVD [2, 6]. Therefore, it is clinically important to better manage hypertension in patients with dyslipidemia, so as to reduce the health and economic burden of CVD [7].

Compared to clinic blood pressure (BP), emerging evidence has consistently demonstrated that 24-hour ambulatory blood pressure monitoring (ABPM) provides superiority in predicting targeted organ damage and cardiovascular events in hypertensive populations [8–11]. The underly-

ing mechanisms are multifactorial. For example, ABPM offers more complete and comprehensive BP information in a longer duration. In addition, ABPM can distinguish hypertensive patterns in terms of the dipping and non-dipping BP pattern within a 24-hour circadian cycle [12, 13].

Prior observational studies indicated that compared to the dipping BP pattern (mean nighttime/daytime BP ratio ≤ 0.9), the non-dipping BP pattern (mean nighttime/daytime BP ratio > 0.9) [14] was more closely associated with CVD risks [15, 16]. Therefore, one might anticipate that in dyslipidemia patients with hypertension, those with the non-dipping BP pattern might also have higher CVD risk compared to their counterparts with the dipping BP pattern. In the present study, we used a cross-sectional design to compare the prevalence of CVD between dyslipidemia patients with dipping and non-dipping BP patterns. From a clinical perspective, such information will help in determining whether correcting the BP pattern would have potential for reducing CVD risk in dyslipidemic patients with hypertension in the future.

Material and methods

Study populations

The present study was approved by the Clinical Ethic Committee of the Third People's Hospital of Huizhou and informed consent was obtained before enrollment. Inclusion criteria were as follows: participants had a documented diagnosis of dyslipidemia (based on either fasting serum low-density lipoprotein cholesterol (LDL-C) level ≥ 3.4 mmol/l or treatment with statins) and hypertension (based on either clinic systolic and/or diastolic BP (SBP/DBP) ≥ 140/90 mm Hg or treatment with anti-hypertensive medications). Exclusion criteria were as follows: subjects did not want to participate in the current study, or had secondary hypertension, familial dyslipidemia, had acute myocardial infarction, ischemic stroke, or congestive heart failure in the last 12 months.

Collection of clinical and laboratory characteristics

Patients' characteristics including age, gender, smoking status, body mass index (BMI, weight in kilograms divided by height in squared meters), and medical histories including diabetes mellitus (DM), coronary heart disease (CHD), ischemic stroke (IS) and chronic kidney disease (CKD) were recorded. Current medication usage was also recorded. Laboratory indexes including fasting serum levels of lipid profiles, glucose and creatinine were extracted from electronic medical documents. All these procedures were performed by two independent investigators.

Parameters of clinic BP and ABPM collection

Clinic BP parameters including SBP and DBP were measured after patients sat quietly for 10 min and three BP readings were obtained at 1-minute intervals, and the last two BP readings were averaged as clinic BP. ABPM parameters including 24-hour SBP and DBP, and daytime (from 8:00 to 22:00) and nighttime (from 22:00 to 8:00) SBP and DBP were collected. In brief, the device used for ABPM measurement was model no. 90207 (Spacelabs Medical Inc, Redmond, Washington, USA). Ambulatory BP was recorded in the non-dominant arm at 20 min intervals during the daytime and at 30 min intervals during the nighttime. Accordingly, patients with a night-day ratio of SBP and/or DBP ≤ 0.90 were defined as having a dipping pattern, and those with a ratio > 0.90 were defined as having a non-dipping pattern [16].

Statistical analysis

Continuous variables were described using mean ± SD and categorical variables were described by the number and frequency of cases. The statistical significance of difference was analyzed using Student's *t*-test for continuous variables and the χ^2 or Fisher exact test for categorical variables. Logistic regression analysis was used to evaluate the associations between dipping and non-dipping hypertension and the prevalence of CVD including CHD and IS. Statistical analysis was computed using SPSS 17.0 (SPSS Inc, Chicago, IL). All of the statistical tests were two-sided and results were considered statistically significant when the *p*-value < 0.05.

Results

Comparisons between dipping and non-dipping hypertensive patients

Clinical characteristics, medications usage and laboratory indices of dipping and non-dipping hypertensive patients are listed in Table I. The mean durations of hypertension in both groups were 5.3 ±2.1 years and 5.6 ±2.4 years, respectively. Compared to the dipping group, patients in the non-dipping group were older, and more likely to be male, smokers, and had a higher serum creatinine level and higher prevalence of CKD (p < 0.05 for all comparisons). Additionally, patients in the non-dipping group also more likely had CHD (39.1% vs. 31.4%, p < 0.05) and CVD (49.3% vs. 40.9%, p < 0.05). No significant between-group differences in current medications usage including the mean numbers and classes of anti-hypertensive medications and lipid profiles were observed.

Table I. Comparisons between dipping and non-dipping hypertensive patients

Characteristics	Dipping (n = 105)	Non-dipping (n = 138)	P-value
Demographics:			
Age [years]	54.5 ±10.8	59.3 ±13.6	0.006
Male, n (%)	55 (52.4)	83 (60.1)	0.018
Smoking, n (%)	49 (46.7)	68 (49.3)	0.046
BMI [kg/m^2]	23.7 ±2.6	24.1 ±3.1	0.270
CHD, n (%)	33 (31.4)	54 (39.1)	0.002
IS, n (%)	10 (9.5)	14 (10.1)	0.722
CVD, n (%)	43 (40.9)	68 (49.3)	0.004
DM, n (%)	27 (25.7)	36 (26.1)	0.383
CKD, n (%)	10 (9.5)	17 (12.3)	0.039
Hypertension duration [years]	5.3 ±2.1	5.6 ±2.4	0.106
Medications:			
Anti-platelet, n (%)	64 (61.0)	89 (64.5)	0.063
Statins, n (%)	57 (54.3)	78 (56.5)	0.109
Anti-hypertension, n (%):	96 (91.4)	127 (92.0)	0.820
ACEi/ARB	68 (64.8)	90 (65.2)	0.446
CCB	22 (21)	28 (20.3)	0.560
Diuretic	37 (35.2)	52 (37.7)	0.094
β-blocker	16 (15.2)	22 (15.9)	0.306
α-blocker	5 (4.8)	9 (6.5)	0.113
Numbers of agents	2.4 ±0.7	2.6 ±0.6	0.645
Anti-diabetes, n (%)	27 (25.7)	34 (24.6)	0.558
Laboratory indexes:			
FPG [mmol/l]	6.0 ±0.9	5.8 ±0.7	0.407
TC [mmol/l]	5.3 ±0.5	5.4 ±0.8	0.624
LDL-C [mmol/l]	3.1 ±0.5	3.2 ±0.6	0.375
HDL-C [mmol/l]	1.1 ±0.3	1.1 ±0.4	0.860
TG [mmol/l]#	1.6 (1.2–3.7)	1.8 (1.1–3.9)	0.443
Creatinine [μmol/l]	90.8 ±11.6	102.4 ±12.2	0.017

FPG – fasting plasma glucose, TC – total cholesterol, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, TG – triglyceride, CVD – CHD plus IS, #TG – median and interquartile, ACEi/ARB – angiotensin converting enzyme inhibitor/ angiotensin receptor blocker, CCB – calcium channel blocker.

Clinic BP and ABPM comparisons in dipping and non-dipping groups

Parameters of clinic BP and ABPM were compared according to the dipping and non-dipping BP patterns. As summarized in Table II, no significant between-group differences in the clinic SBP and DBP were observed. However, compared to the dipping group, 24-hour SBP, nighttime SBP and DBP, night-day ratio of SBP and DBP were all significantly higher in the non-dipping group versus the dipping group ($p < 0.05$ for all comparisons).

Associations of BP patterns and prevalence of CVD

Associations of BP patterns and prevalence of CVD were evaluated by logistic regression analysis. As shown in Table III, the associations of night-day ratios of SBP and DBP with prevalent CVD

Table II. Clinic BP and ABPM comparisons in dipping and non-dipping groups

Characteristics	Dipping (n = 105)	Non-dipping (n = 138)	P-value
Clinic:			
SBP [mm Hg]	134 ±17	131 ±20	0.755
DBP [mm Hg]	80 ±12	82 ±15	0.406
ABPM:			
24-hour:			
SBP [mm Hg]	120 ±13	126 ±16	0.023
DBP [mm Hg]	74 ±12	74 ±10	0.630
Daytime:			
SBP [mm Hg]	126 ±15	125 ±13	0.843
DBP [mm Hg]	76 ±9	75 ±12	0.308
Nighttime:			
SBP [mm Hg]	114 ±11	120 ±10	< 0.001
DBP [mm Hg]	69 ±8	73 ±10	0.003
Night-day ratio:			
SBP	0.83 ±0.04	0.97 ±0.05	< 0.001
DBP	0.81 ±0.07	0.95 ±0.04	< 0.001

SBP – systolic blood pressure, DBP – diastolic blood pressure, ABPM – ambulatory blood pressure monitoring.

Table III. Association of BP pattern and prevalence of CVD

Model		Odds ratio	95% confidence interval	P-value
Dipping pattern:				
Model 1	Night-day ratio of SBP	1.34	1.18–1.96	< 0.001
	Night-day ratio of DBP	1.16	0.94–1.63	0.089
Model 2	Night-day ratio of SBP	1.18	1.09–1.46	0.007
	Night-day ratio of DBP			NS
Model 3	Night-day ratio of SBP	1.09	1.02–1.34	0.011
	Night-day ratio of DBP			NS
Non-dipping pattern:				
Model 1	Night-day ratio of SBP	2.01	1.47–2.69	< 0.001
	Night-day ratio of DBP	1.45	1.17–1.85	0.006
Model 2	Night-day ratio of SBP	1.89	1.43–2.11	< 0.001
	Night-day ratio of DBP	1.36	1.17–1.90	0.014
Model 3	Night-day ratio of SBP	1.72	1.33–2.06	< 0.001
	Night-day ratio of DBP	1.23	1.05–1.66	0.033

Model 1 adjusted for age and gender; Model 2 additionally adjusted for smoking, BMI, DM, CKD and LDL-C; Model 3 adjusted for clinic SBP and DBP; NS – non-significant.

were assessed in dipping and non-dipping groups, respectively. In the dipping group, only night-day ratio of SBP was significantly associated with prevalent CVD after adjusting for potential risk factors, with an odds ratio (OR) of 1.09 (95% confidence interval (CI) of 1.02–1.34). Nevertheless, in the non-dipping group, both night-day ratio of SBP and DBP were significantly associated with

prevalent CVD after being extensively adjusted for potential risk factors including clinic SBP and DBP, with an OR of 1.72 (95% CI: 1.33–2.06) and 1.23 (95% CI: 1.05–1.66), respectively.

Discussion

Our present study shows that in dyslipidemia patients with hypertension, the night-day ratio of SBP and DBP measured by 24-hour ABPM could be used to complement clinic SBP and DBP in evaluating CVD risk. In addition, the non-dipping BP pattern appears to be more closely related to prevalent CVD compared to the dipping BP pattern in dyslipidemia patients. Future randomized controlled trials are warranted to investigate whether correcting the BP pattern will reduce cardiovascular events in dyslipidemia patients with hypertension. Specifically, we can enroll dyslipidemia patients with the non-dipping BP pattern and randomly assign them to an active group and a placebo group to evaluate whether reversing the non-dipping BP pattern by using nighttime anti-hypertensive medications would reduce cardiovascular events compared to the placebo group.

Owing to the high proportion of population attributable risk accounted for both dyslipidemia and hypertension [2], it is clinically relevant to investigate whether different BP patterns would have differing effects on cardiovascular systems in patients with dyslipidemia. Notably, the non-dipping BP pattern is better than the dipping BP pattern in relation to cardiovascular events in general hypertensive patients [17, 18]. Consistent with previous findings, our present study also showed that in patients with dyslipidemia, the non-dipping BP pattern was better than the dipping BP pattern in relation to prevalent CVD after extensively adjusting for traditional risk factors including age, smoking, lipid profiles, DM, CKD, as well as clinic SBP and DBP. The following possibilities might be ascribed to these findings. First, blunted BP reduction during nighttime is commonly associated with enhanced sympathetic activity, which in turn increases heart rate and cardiac output [19–21]. Of note, these hemodynamic alterations are detrimental to cardiovascular systems, thereby increasing CVD risk. Second, obstructive sleep apnea (OSA) is closely associated with non-dipping hypertension. It is known that OSA is significantly associated with systemic inflammation, oxidative stress and endothelial dysfunction [19]. Therefore, it is conceivable that the effects of the non-dipping hypertensive pattern exerted on cardiovascular systems might be partially associated with unrecognized OSA. Third, the predictive value of daytime BP may be attenuated by its higher variability as compared to nighttime BP [20–22], which renders nighttime BP measured by 24-hour ABPM essential for CVD risk discrimination.

We observed significant differences in clinical characteristics between dipping and non-dipping BP pattern groups. For example, patients with the non-dipping pattern were older and more likely to be male and smokers and had higher prevalence of CKD, suggesting that these patients per se might be at a higher CVD risk than their dipping counterparts. We also observed that clinic SBP and DBP were comparable between the dipping and non-dipping groups. Nevertheless, there were significant differences in 24-hour BP parameters between these two groups. As presented in Table II, both nighttime SBP and DBP were significantly higher in the non-dipping group, while no significant between-group differences were observed in daytime SBP and DBP, further supporting the notion that nighttime BP might be more closely associated with CVD than daytime BP [16], and 24-hour ABPM is essential for dyslipidemia patients with hypertension in terms of CVD risk assessment [23].

There are several limitations of our present study. First, the cross-sectional design could not allow us to infer a causal relationship between non-dipping BP pattern and prevalent CVD in patients with dyslipidemia. However, emerging evidence has shown that blunted nocturnal BP fall was associated with greater CVD risk. Second, the relatively small number of IS cases might not allow us to observe any significant difference between the dipping and non-dipping groups. However, owing to the similar pathophysiological mechanisms underlying CHD and IS, it was possible that the non-dipping pattern was more closely related to IS than the dipping pattern. Third, as we have mentioned, OSA is highly prevent in non-dipping hypertensive patients. However, we did not evaluate OSA in the current study. Therefore, we could not adjust OSA for the association of non-dipping BP pattern and prevalent CVD. In our ongoing study, we will expand our studied sample size and evaluate OSA prospectively, so as to evaluate the effects of OSA on BP pattern change at night as well as to evaluate the association between non-dipping BP pattern and CVD risk in dyslipidemic patients with adjustment for OSA. Last but not least, our participants had comorbidities such as CHD, IS, diabetes mellitus and CKD, which might somewhat influence BP pattern and its association with prevalent CVD. Prospective cohort studies are needed to evaluate whether BP pattern can be used to predict the future incidence of CVD in patients with dyslipidemia but without prevalent CVD at baseline.

In conclusion, our present study reveals that in patients with dyslipidemia, the non-dipping

BP pattern is better than the dipping pattern in relation to prevalent CVD, and 24-hour ABPM measurement is better than clinic BP in relation to prevalent CVD. Future research is necessary to investigate whether reversing the non-dipping pattern will reduce the CVD risk in patients with dyslipidemia.

Acknowledgments

We are indebted to Dr. Ying Wang for her help in conducting statistical analysis for our paper.

Current study was supported from The Technology Grant of Huizhou (170512101740855).

Conflict of interest

The authors declare no conflict of interest.

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