ORIGINAL ARTICLE

Associations of systolic and diastolic blood pressure night-to-day ratios with atherosclerotic cardiovascular diseases

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Our objective was to evaluate the associations of the systolic and diastolic blood pressure night-to-day ratios (SBP-NDR and DBP-NDR) with composite atherosclerotic cardiovascular diseases (ASCVDs) comprising coronary heart disease (CHD) and ischemic stroke (IS) cases, respectively. The clinical conditions associated with SBP-NDR and DBP-NDR were also evaluated. A total of 401 patients who underwent 24-h ambulatory BP monitoring were enrolled. In general, the mean age was 59.7 ± 14.7 years and male subjects accounted for 59.1% of the study subjects. Regarding the ASCVD risk factors, 17.0% of the study subjects smoked, 5.2% abused alcohol, 2.0% had a family history of ASCVD, 23.3% had diabetes and 96.0% had dyslipidemia. Fifty (12.5%) and 128 (31.9%) study subjects had a previous diagnosis of CHD and IS, respectively. Dipper and non-dipper pattern-specific differences in clinical characteristics between the SBP-NDR and DBP-NDR categories were observed. The multiple linear regression analysis showed that advanced age, smoking, CHD and IS were positively associated with SBP-NDR and statins were inversely associated with SBP-NDR; only IS was positively associated with DBP-NDR. The logistic regression analysis showed that after adjusting for the covariates of age, smoking, alcohol abuse, diabetes, hypertension, dyslipidemia, and SBP and DBP at admission, only DBP-NDR remained significantly associated with composite ASCVD, with an odds ratio of 1.029 (95% confidence interval 1.002–1.056, $P = 0.038$). There were significant differences in the associations of SBP-NDR and DBP-NDR with composite ASCVD. Clinical conditions independently associated with SBP-NDR and DBP-NDR were also somewhat different. In a specific population group, DBP-NDR may be superior to SBP-NDR with respect to screening for ASCVD.

INTRODUCTION

Hypertension has become a major public health problem in China, owing to its significant contribution to the increasing incidence and prevalence of atherosclerotic cardiovascular diseases (ASCVDs), such as coronary heart disease (CHD) and ischemic stroke (IS), in recent decades.[1–3] It is therefore clinically important to screen and identify hypertensive subjects who are at high cardiovascular risk, to apply effective and timely preventions that will reduce ASCVD incidence.

Clinic blood pressure (BP) has been shown to be associated with cardiovascular outcomes[4,5] and it has been used commonly in clinical practice to diagnose hypertension and to evaluate hypertension severity. However, there are several drawbacks of clinic BP measurement, such as a limited number of BP readings and the inability to assess BP variability over a period of time. Compared with clinic BP measurement, 24-h ambulatory BP monitoring (ABPM) has multiple

advantages, including that it allows the assessment of hypertension severity, BP variability and therapeutic efficacy for over 24 h.[6] Moreover, it is reported that ABPM is superior to clinic BP in predicting target organ damage and cardiovascular outcomes,[7,8] and these benefits are attributed to its capacity to assess nighttime BP levels and discriminate BP patterns in terms of dippers and non-dippers.[8,9]

In brief, a nocturnal BP decline is a normal physiological regulation called the dipper BP pattern and blunted decline or rise in nocturnal BP is termed the non-dipper pattern, which has been revealed to be significantly associated with adverse cardiovascular outcomes.[10,11] However, whether there are differences in the associations of blunted systolic and diastolic BP (SBP and DBP) decline with ASCVD and whether there are differences in the clinical conditions associated with blunted SBP and DBP decline have not been sufficiently investigated. Moreover, such investigations in Chinese populations are limited. As

24-h ABPM is increasingly applied and BP patterns are predictors of cardiovascular outcomes, we therefore conducted a cross-sectional study on 401 patients who were referred for 24-h ABPM in the inpatient department of the Guangdong General Hospital, to address the two issues listed above.

SUBJECTS AND METHODS

Study subjects
A total of 401 patients who had undergone a 24-h ABPM in our inpatient department were enrolled after oral informed consent was obtained. This study was approved by the Research Ethics Committee of the Guangdong General Hospital. Patients were enrolled from 1 January 2015 to 31 December 2015. In brief, there were two inclusion criteria: study subjects underwent a 24-h ABPM and the data of interest were available; those who did not wish to take part in the present study were excluded. ABPMs were performed on the study subjects, primarily because there was a need to evaluate their 24-h BP variability while they were treated with anti-hypertensive drug therapy; a minority of the study subjects were suspected of hypertension and underwent a 24-h ABPM to reach a definite diagnosis.

BP measurement
BP measurement at admission was performed after the patients sat quietly for 10 min by using the Omron HEM-7051 device (Omron HealthCare, Kyoto, Japan) and heart rate at admission was simultaneously recorded. For the 24-h ambulatory BP measurement, we used a portable BP monitoring device (model 90207, Space-Labs Medical Inc., Redmond, WA, USA). Ambulatory BP was recorded from the non-dominant arm for 24 h at 20-min intervals during the day (0600–2200 h) and at 30-min intervals during the night (2200–0600 h). Continuous SBP and DBP night-to-day ratios (SBP-NDR and DBP-NDR) were calculated by dividing the nighttime SBP and DBP values by the daytime SBP and DBP values, respectively. In brief, subjects with SBP-NDR or DBP-NDR ⩽ 0.90 were defined as having a dipper BP pattern and > 0.90 had a non-dipper BP pattern.[6]

Clinical and laboratory data collection
The clinical data, including demographics (such as age, gender, smoking status, alcohol abuse and family history of ASCVD), previous medical history (including hypertension, diabetes, dyslipidemia, chronic kidney disease, CHD and IS) and present medication use, were recorded on a case report form. Diagnosis of hypertension, diabetes or dyslipidemia was based on self-report or the use of corresponding medications. Diagnosis of CHD was based on clinical symptoms combined with a coronary computed tomography angiography or coronary artery angiography, and diagnosis of IS was based on a focal neurological deficit combined with a computed tomography scan. Fasting venous blood was sampled for measurements of creatinine, fasting plasma glucose, glycated hemoglobin (HbA1c) and the lipid profile.

Statistical analysis
Standard descriptive statistics were applied in the analysis. Continuous variables were described using the mean and s.d. and categorical variables were described by the number and percentage of cases. The differences were analyzed using the independent T-test for continuous variables and χ^2-test or Fisher's exact test for categorical variables. The associations of SBP-NDP and DBP-NDR with clinical conditions were assessed by multiple linear regression analyses. Logistic regression analyses were used to evaluate the associations of SBP-NDR and DBP-NDR with composite ASCVD, including CHD and IS. All of the statistical analyses were computed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). All of the statistical tests were two-sided and considered statistically significant when the P-value was < 0.05.

RESULTS

General characteristics of study subjects
Among the 401 study subjects, 263 (65.5%) had a previous diagnosis of hypertension. The mean age was 59.7 ± 14.7 years and male subjects accounted for 59.1% ($n = 237$). SBP and DBP at admission were 139.1 ± 20.6 and 82.4 ± 15.0 mm Hg, respectively, and heart rate at admission was 76.9 ± 12.5 beats per minute. The mean 24-h SBP and DBP were 132.7 ± 20.2 and 79.7 ± 12.1 mm Hg, respectively, and the mean 24-h heart rate was 72.2 ± 10.2 beats per minute. Regarding ASCVD risk factors, 17.0% of the study subjects smoked, 5.2% abused alcohol, 2.0% had a family history of ASCVD, 23.3% had diabetes and 96.0% had dyslipidemia. Fifty (12.5%) and 128 (31.9%) study subjects had a previous diagnosis of CHD and IS, respectively, and 13 (3.2%) had a diagnosis of chronic kidney disease.

Pattern-specific differences in clinical characteristics by SBP-NDR and DBP-NDR categories
Based on SBP-NDR, 74.8% of the 401 study subjects had a non-dipper BP pattern. Compared with subjects who had a dipper BP pattern, those who had a non-dipper BP pattern had higher levels of fasting plasma glucose and blood urine nitrogen. In addition, both mean 24 h SBP and DBP, and both SBP-NDR (0.98 ± 0.06 *vs.* 0.86 ± 0.04) and DBP-NDR (0.97 ± 0.08 *vs.* 0.87 ± 0.06) were also significantly higher in the non-dipper BP pattern group than the dipper BP pattern group ($P < 0.05$ for all comparisons). Study subjects with a non-dipper BP pattern were more frequently smokers (19.7% *vs.* 8.9%, $P < 0.05$) and had a higher frequency of diabetes (26.0% *vs.* 14.9%, $P < 0.05$). No significant differences in IS (29.7% *vs.* 32.7%), CHD (7.9% *vs.* 14.0%) and chronic kidney disease (2.0% *vs.* 3.7%) were observed between subjects with dipper and non-dipper BP patterns.

Based on DBP-NDR, 66.8% of the 401 study subjects had a non-dipper BP pattern. Compared with subjects who had a dipper BP pattern, those who had a non-dipper BP pattern had higher fasting plasma glucose levels. In addition, SBP at admission, mean 24 h SBP and both SBP-NDR (0.98 ± 0.07 *vs.* 0.89 ± 0.05) and DBP-NDR (0.98 ± 0.06 *vs.* 0.85 ± 0.05) were also significantly higher in the non-dipper BP pattern group than in the dipper BP pattern group ($P < 0.05$ for all comparisons). The study subjects with a non-dipper BP pattern had significantly higher frequencies of hypertension (69.0% *vs.* 58.6%, $P < 0.05$) and CHD (14.9% *vs.* 7.5%, $P < 0.05$) and IS was marginally higher (35.1% *vs.* 25.6%, $P = 0.054$). (See Table 1).

Clinical conditions associated with SBP-NDR and DBP-NDR
Both SBP-NDR and DBP-NDR were analyzed as continuous variables and a multiple linear regression analysis was performed. As shown in Table 2, we observed that advanced age, smoking, CHD and IS were positively associated with SBP-NDR, whereas statins were inversely associated with SBP-NDR. In addition, only IS was positively associated with DBP-NDR.

Associations of SBP-NDR and DBP-NDR with composite ASCVD
Because of the relatively small number of CHD and IS cases in the present study, we defined composite ASCVD as the combination of these cases to decrease the likelihood of logistic model instability when CHD and IS were analyzed separately. In brief, both SBP-NDR and DBP-NDR were analyzed as continuous variables. As presented in Table 3, the logistic regression analysis showed that, in the unadjusted model, both SBP-NDR and DBP-NDR were positively and comparably associated with composite ASCVD. In model 1, after adjustment for age, gender, smoking, alcohol abuse and family history, both SBP-NDR and DBP-NDR were still significantly associated with composite ASCVD. In model 2, after further adjustment for diabetes, hypertension and dyslipidemia, the association of SBP-NDR with composite ASCVD was attenuated and nonsignificant, whereas DBP-NDR remained significantly associated with composite ASCVD with an

Table 1 Pattern-specific differences by SBP-NDR and DBP-NDR categories

Variables	SBP-NDR			DBP-NDR		
	Dipper (n = 101)	Non-dipper (n = 300)	P-value	Dipper (n = 133)	Non-dipper (n = 268)	P-value
Age (years)	59.0±14.0	59.9±15.0	0.543	59.5±15.5	59.8±14.4	0.151
Male, n (%)	58 (57.4)	179 (59.7)	0.692	72 (54.1)	165 (61.6)	0.154
Smoking, n (%)	9 (8.9)	59 (19.7)	0.013	20 (15.0)	48 (17.9)	0.470
Alcohol abuse, n (%)	2 (2.0)	19 (6.3)	0.089	8 (6.0)	13 (4.9)	0.622
Family history, n (%)	1 (1.0)	7 (2.3)	0.404	2 (1.5)	6 (2.2)	0.620
TC (mmol l^{-1})	4.92±1.19	4.94±1.23	0.654	5.00±1.15	4.91±1.26	0.212
LDL-C (mmol l^{-1})	2.86±0.98	2.88±0.96	0.807	2.88±0.90	2.88±0.99	0.161
HDL-C (mmol l^{-1})	1.13±0.30	1.10±0.29	0.537	1.14±0.31	1.09±0.28	0.224
FPG (mmol l^{-1})	5.30±1.37	5.78±2.08	0.002	5.34±1.39	5.82±2.14	0.002
HbA1c (%)	6.03±1.29	6.35±1.57	0.091	6.13±1.24	6.33±1.62	0.074
BUN (mmol l^{-1})	4.75±1.30	5.17±1.98	0.010	4.94±1.61	5.13±1.94	0.087
Cr (μmol l^{-1})	78.59±26.22	82.24±42.48	0.169	76.64±26.70	86.63±43.71	0.155
SBP at admission (mm Hg)	136.9±18.9	139.8±21.1	0.095	136.2±18.3	140.5±21.5	0.013
DBP at admission (mm Hg)	82.5±14.5	82.4±15.1	0.589	80.8±14.5	83.2±15.1	0.549
HR at admission (bpm)	76.6±11.7	77.0±12.8	0.403	76.3±12.3	77.3±12.7	0.994
Mean 24 h SBP (mm Hg)	126.4±16.3	134.8±21.0	0.005	126.9±18.2	135.6±20.6	0.046
Mean 24 h DBP (mm Hg)	77.4±10.8	80.5±12.4	0.028	76.5±11.3	81.3±12.2	0.190
Mean 24 h HR (bpm)	72.2±8.7	72.3±10.7	0.045	72.1±9.2	72.3±10.8	0.062
SBP-NDR	0.86±0.04	0.98±0.06	<0.001	0.89±0.05	0.98±0.07	0.021
DBP-NDR	0.87±0.06	0.97±0.08	0.047	0.85±0.05	0.98±0.06	0.001
HR-NDR	0.87±0.07	0.90±0.07	0.782	0.88±0.07	0.91±0.07	0.712
DM, n (%)	15 (14.9)	78 (26.0)	0.022	28 (21.1)	65 (24.3)	0.475
HTN, n (%)	61 (60.4)	202 (67.3)	0.204	78 (58.6)	185 (69.0)	0.039
Dyslipidemia, n (%)	95 (94.1)	290 (96.7)	0.247	129 (97.0)	256 (95.5)	0.479
CKD, n (%)	2 (2.0)	11 (3.7)	0.408	3 (2.3)	10 (3.7)	0.432
IS, n (%)	30 (29.7)	98 (32.7)	0.581	34 (25.6)	94 (35.1)	0.054
CHD, n (%)	8 (7.9)	42 (14.0)	0.110	10 (7.5)	40 (14.9)	0.035
Anti-platelet, n (%)	41 (40.6)	133 (44.3)	0.512	48 (36.1)	126 (47.0)	0.038
Statins, n (%)	64 (63.3)	166 (55.3)	0.158	74 (55.6)	156 (58.2)	0.624
ACEI, n (%)	3 (3.0)	19 (6.3)	0.199	5 (3.8)	17 (6.3)	0.285
ARB, n (%)	22 (21.8)	91 (30.3)	0.098	31 (23.3)	82 (30.6)	0.127
CCB, n (%)	30 (29.7)	93 (31.1)	0.792	39 (29.5)	84 (31.3)	0.714
Diuretic, n (%)	5 (5.0)	30 (10.0)	0.120	10 (7.5)	25 (9.3)	0.546
Beta-blocker, n (%)	7 (6.9)	37 (12.3)	0.133	11 (8.3)	33 (12.3)	0.223

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; bpm, beats per minute; BUN, blood urine nitrogen; CCB, calcium channel blocker; CHD, coronary heart disease; CKD, chronic kidney disease; Cr, creatinine; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; HTN, hypertension; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; NDR, night-to-day ratio; SBP, systolic blood pressure; TC, total cholesterol.

Table 2 Clinical conditions associated with SBP-NDR and DBP-NDR

Variables	SBP-NDR*100		DBP-NDR*100	
	Coefficient β (95% CI)	P-value	Coefficient β (95% CI)	P-value
Age	0.077 (0.008–0.145)	0.028		NS
Male gender		NS		NS
Smoking	3.348 (0.814–5.882)	0.010		NS
Alcohol abuse		NS		NS
Statins	−3.107 (−5.550–0.663)	0.013		NS
Anti-HTN drugs		NS		NS
DM		NS		NS
Dyslipidemia		NS		NS
CKD		NS		NS
CHD	3.364 (0.495–6.233)	0.022		NS
IS	3.262 (1.002–5.522)	0.005	2.770 (0.263–5.277)	0.030

Abbreviations: CI, confidence interval; CHD, coronary heart disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; IS, ischemic stroke; NDR, night-to-day ratio; NS, nonsignificant; SBP, systolic blood pressure.

Table 3 Associations between SBP-NDR and DBP-NDR with composite ASCVD

	SBP-NDR*100		DBP-NDR*100	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Unadjusted	1.039 (1.011–1.067)	0.006	1.034 (1.009–1.060)	0.008
Model 1	1.032 (1.003–1.062)	0.032	1.027 (1.001–1.054)	0.042
Model 2		NS	1.028 (1.001–1.055)	0.043
Model 3		NS	1.029 (1.002–1.056)	0.038

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; DBP, diastolic blood pressure; NDR, night-to-day ratio; NS, non-significant; OR, odds ratio; SBP, systolic blood pressure.

odds ratio of 1.028 and 95% confidence interval of 1.001–1.055 ($P = 0.043$). In model 3, after additional adjustment for SBP and DBP levels at admission, the association between DBP-NDR and composite ASCVD was stable with an odds ratio of 1.029 (95% confidence interval 1.002–1.056, $P = 0.038$).

DISCUSSION

The results from our present preliminary study showed that there were substantially significant differences in the associations of SBP-NDR and DBP-NDR with composite ASCVD. In addition, clinical conditions independently associated with SBP-NDR and DBP-NDR were also somewhat different. These findings from Chinese populations are novel and merit further investigation in a prospective and large sample size population study.

Compared with conventional clinic BP measurement, 24-h ambulatory BP measurement has multiple advantages. It can be used to improve diagnostic accuracy by excluding 'white-coat' hypertension and identifying masked hypertension. Moreover, it provides information about BP levels over 24 h and BP patterns in terms of dippers and non-dippers. In recent decades, a substantial number of epidemiological studies revealed that a 24-h ABPM could provide a more accurate prediction of target organ damage and cardiovascular outcomes. For example, in a population of 1047 untreated Chinese hypertensive patients, Fang-Fei Wei et al.[12] reported that the 24-h SBP level predicted target organ damage more accurately than conventional BP measurement. Staessen et al.[7] also recruited untreated hypertensive patients as study subjects and the results from their study showed that nighttime SBP more accurately predicted cardiovascular endpoints than daytime SBP; a higher SBP-NDR was also associated with an increased cardiovascular risk. The results from Dolan Eamon et al.[8] supported the notion that blunted nocturnal BP decline was a potent predictor of cardiovascular outcome, and that the 24-h ABPM offered comprehensive and integrative BP information on the cardiovascular system and thereby refined cardiovascular risk stratification.[13] The results from our present cross-sectional study confirmed a close association of continuous SBP-NDR and DBP-NDR with cardiovascular outcomes. Moreover, we additionally observed that DBP-NDR seemed to be superior to SBP-NDR in relation to composite ASCVD. It is conceivable that the pattern-specific differences in clinical characteristics between the SBP-NDR and DBP-NDR categories, as listed in Table 1, might partially explain the discrepancies observed between SBP-NDR and DBP-NDR. However, owing to the relatively small number of ASCVD cases, our present finding might not be significant and future, large-sample-size prospective studies are needed to clarify this preliminary evidence.

Owing to the significant pathophysiological effects of blunted nocturnal BP decline on the cardiovascular system[14,15], it is relevant to evaluate clinical conditions associated with a non-dipper BP pattern. In a large cohort of Spanish hypertensive patients, Sierra et al.[16] reported that in both treated and non-treated patients, advanced age, obesity, diabetes mellitus and overt cardiovascular or renal diseases were associated with a blunted nocturnal BP decline. Similar to these previous findings, we also observed that advanced age and overt cardiovascular diseases such as CHD and IS were associated with a blunted nocturnal BP decline. Nonetheless, some differences in the associations of clinical conditions with SBP-NDR and DBP-NDR were also observed, as seen in Table 2. Pattern-specific differences in clinical characteristics between the SBP-NDR and DBP-NDR categories might also partially explain these observations and a future, large-sample-size prospective study could provide a more comprehensive picture about the differences in associations of SBP-NDR and DBP-NDR with clinical conditions.

Several limitations should be taken into account when interpreting our results. First, this was a cross-sectional study and the results from the present study should not be used to draw causal conclusions. Nonetheless, the novel findings from Chinese populations may be useful for hypothesis generation. Second, the relatively small number of study subjects may not allow us to comprehensively compare the pattern-specific differences in clinical characteristics between the SBP-NDR and DBP-NDR categories. Our ongoing study, which plans to recruit more populations referred for 24-h ABPM, may help us further clarify these pattern-specific differences. Third, the number of CHD and IS cases was also relatively small and the multivariable-adjusted odds ratio estimates of SBP-NDR and DBP-NDR might be unstable. Therefore, we combined CHD and IS cases to form a composite ASCVD group, to reduce the likelihood of model instability. Fourth, it is well known that sleep quality and obstructive sleep apnea have a role in BP pattern and thereby affect the associations of SBP-NDR and DBP-NDR with ASCVD[17]. However, we lacked data about sleep quality and obstructive sleep apnea prevalence in our present study and readers should pay attention to this limitation. In future prospective studies, it is necessary and important to evaluate these two major aspects to improve predictive accuracy. Lastly, the present study only recruited Chinese subjects and this was a single-center study; therefore, these findings should not be extrapolated to other populations.

CONCLUSION

The findings from our preliminary study have implications for daily clinical practice. Compared with the readily available and free clinic BP measurement, our results justify the broad application of 24-h ABPM to improve both diagnostic and predictive accuracies. In a specific population group, DBP-NDR may be superior to SBP-NDR with respect to screening for ASCVD, and both SBP-NDR and DBP-NDR may be beneficial for risk stratification refinement. Certain clinical conditions may predispose hypertensive subjects to the development of either SBP-specific non-dipper patterns or DBP-specific non-dipper patterns, and it is clinically relevant to identify these clinical conditions to prevent or reverse non-dipper BP patterns.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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