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Relationship between carotid artery sclerosis and blood pressure variability in essential hypertension patients

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ABSTRACT

Objectives: This study aimed to investigate the relationship between the presence of carotid arteriosclerosis (CAS) and blood pressure variability (BPV) in patients with essential hypertension.
Methods: One hundred and forty four essential hypertension patients underwent ambulatory BP monitoring for 24 h after hospitalization. Common BPV metrics were calculated. General clinical parameters, including age, gender, height, weight, history of coronary heart disease, stroke, diabetes, hypertension, smoking and drink, were recorded. Biochemical indices were obtained from a blood test. Carotid intima-media thickness (IMT) and carotid plaques were assessed to separate patients into a non-CAS group (IMT≤0.9 mm; n=82) and a CAS group (IMT > 0.9 mm; n=62). BPV metrics and clinical parameters were analyzed and compared between the two groups. Multivariate logistic regression analysis was performed to determine the associated risk factors of CAS.
Results: Multivariate logistic regression analysis revealed that two BPV metrics, the standard deviation of daytime systolic blood pressure (SSD) (OR: 1.587, 95%CI: 1.242–2.028), the difference between average daytime SBP and nighttime SBP (OR: 0.914, 95%CI: 0.855–0.977), as well as three clinical parameters (age, OR: 1.098, 95%CI: 1.034–1.167; smoking, OR: 4.072, 95%CI: 1.466–11.310, and fasting blood glucose, OR: 2.029, 95%CI: 1.407–2.928), were significant factors of CAS in essential hypertension patients.
Conclusion: SSD, in combination with the ageing, smoking and FBG, has been identified as risk factors for CAS in patients with essential hypertension.

1. Introduction

Carotid atherosclerosis (CAS) is the pathological basis of cardiovascular and cerebrovascular diseases. Many clinical and physiological factors are significantly associated with CAS, including ageing, smoking, hypertension, diabetes. Among them, hypertension is one of the most closely related to CAS [1,2]. Published studies have confirmed that most patients with hypertension have different degrees of CAS [3,4].

Patients with CAS normally have reduced blood pressure (BP) regulation because carotid sinus and aortic arch baroreflex play important roles in the regulation of cardiovascular reflex. The main clinical symptoms include either too high or too low BPs with large BP fluctuation, namely increased BPV. In general, patients with CAS have the carotid intima-media thickness (IMT) more than 0.9 [5–7]. Recent study has reported that daytime and all-day (24 h) systolic blood pressure variability (SBPV) in hypertensive patients are closely related to IMT [8], and SBPV is a good predictor of IMT progression. The clinical significance of BPV has become more attractive to researchers [9–11]. However, the relationship between different BPV metrics and CAS has not been fully agreed [8,12], which requires further and comprehensive investigation.

Many studies have reported that BPV is a risk predictor for organ damage, and considered that BPV is more valuable than increased blood pressure (BP), leading to the suggestion that reducing BPV is more important than lowering BP [9–11,13–15]. Recent research has also suggested that BPV is higher in hypertensive patients than in the healthy subjects [9–11]. Thus, controlling BPV has become a critical

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approach for BP management in hypertensive patients and patients with atherosclerotic diseases.

BPV has been defined in different ways depending on the time duration, including: very short-term (beat-to-beat), short-term (minute-to-minute or reading-to-reading within a 24-h period), middle-term (day-to-day), long-term (visit-to-visit and seasonal) [9–11], from which different BPV metrics have been derived, including the standard deviations (SD) of systolic BP (SBP), diastolic BP(DBP) and pulse pressure (PP), as well as the variability uncorrelated with mean BP [9–11]. In addition, most studies mainly focused on the increased BPV while ignoring the clinical significance of decreased BPV. Most of current BPV metrics are consistent, and have positive correlation with target organ damage. However, some studies suggested that low-reactive BPV (such as blunted surge, nocturnal hypertension, orthostatic hypotension) is also a risk factor of cardiovascular disease, which is also associated with target organ lesions of hypertensive patients. Therefore, it is necessary to study hyporeactive BPV indices and explore its relationship with hypertensive atherosclerosis [16,17].

Various factors, including neuroendocrine factors, vascular wall elasticity, environmental factors, emotional turmoil and sudden movements, affect BPV values [9–11]. Although many studies have provided evidence that CAS is closely associated with BPV [13–15,18], the relationship between CAS and BPV has not been quantified. In addition, different studies have used different BPV indices. This study aimed to explore the relationship between BPV metrics and the degree of CAS in patients with essential hypertension.

2. Methods

2.1. Patients

The study recruited 144 essential hypertension patients who were hospitalized in the Department of Neurology and Department of Cardiology, Weihai Central Hospital Affiliated to Qingdao University Medical College. There were 80 male and 64 female. Their age range was 45–89 year (66 ± 9 year). This study was approved by the College Ethics Committee of Weihai Central Hospital Affiliated to Qingdao University Medical College.

The diagnosis of essential hypertension was based on the criteria reported in the literature [14]. Specifically, all patients underwent manual BP measurements more than three times on three different days. Fifty five patients without receiving any antihypertensive drug treatment whose average SBP was over 140 mmHg and/or a DBP over 90 mmHg were diagnosed as essential hypertension. Ninety patients with a history of hypertension who were taking antihypertensive drug treatment and had SBP lower than 140/90 mmHg were also considered as essential hypertension and included in the study.

The exclusion criteria included: secondary hypertension, younger than 18 years, BP values higher than 220/110 mmHg without taking antihypertensive drugs. Patients who had any of the following conditions were also excluded: acute cerebrovascular disease; severe heart disease, acute heart failure, severe arrhythmias, severe valvular heart disease, recent or just occurred myocardial infarction, cirrhosis of the liver and severe kidney dysfunction, a variety of acute and chronic nephritis, nephrotic syndrome, acute and chronic renal failure, various acute and chronic infectious diseases, a variety of autoimmune diseases, hyperthyroidism, pregnancy, malignant tumors, serious hematological diseases and recent trauma and surgery.

2.2. Clinical parameters

Clinical parameters, including age, gender, height, and weight, were recorded, as well as the history of coronary heart disease, stroke, diabetes, hypertension, smoking and drink. Blood test was taken to measure the levels of triglyceride (TG), total cholesterol(TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), fasting blood glucose (FBG), uric acid, high-sensitivity C-reactive protein(hs-CRP), homocysteine (HCY), glomerular filtration rate (GFR), fibrinogen and urine protein.

2.3. CAS diagnosis

The Aplio 80color Doppler ultrasound device (Toshiba, Japan) with a 10 MHz probe was used to determine the presence of CAS by an experienced clinical staff. Bilateral intima-media thickness (IMT) of the carotid artery vessel wall was measured. The larger bilateral IMT value was used to divide the patients into a non-CAS group (IMT≤0.9 mm; n=82) and a CAS group (IMT > 0.9 mm; n=62).

2.4. Ambulatory BP monitoring

All the patients were asked to cease taking any antihypertensive drugs after hospitalization. Three to five days later, a standard 24-h ambulatory BP monitoring was performed for each patient for 24 h, from which the clinically reliable BP in the absence of medication was obtained. In all cases, the non-dominant upper arm of the patient was used in the BP measurement. While the cuff was inflated and deflated, the patient was advised to keep his/her arm relaxed and avoid movement. The BP measurement interval was 30 min during the daytime (6:00–22:00), and the nighttime (22:00–6:00) interval was 1 h. The measurement successful rate threshold of 85% was used to determine whether a repeat measurement should be taken on alternative days.

During the hospitalization, the patients were asked to undertake normal activities, but to avoid strenuous exercise and anything that might cause adverse mood swings. They were also advised to avoid alcohol, coffee, and tea during the 24 h BP measurement period. Based on the recorded BP values from each patient, the BPV metrics were calculated, including the SD of 24 h SBP, SD of 24 h DBP, SD of daytime SBP, SD of daytime DBP, SD of night SBP, SD of night DBP, the difference between daytime SBP and nighttime SBP (dSBP) and the difference between daytime DBP and nighttime DBP (dDBP).

The percentage of patients with BP circadian rhythm was calculated, which was defined as the nocturnal BP decreases by 10–20%. In addition, the percentage of patients with morning BP surge (MBPS) was also calculated, which was verified if the BP within 2 h after arousal was more than 35 mmHg to the nocturnal BP.

2.5. Statistical analysis

The data were analyzed using the SPSS19.0 software (Armonk, NY: IBM Corp.). Measurement data that conformed to a normal distribution were presented as the mean ± SD, and comparisons between the two groups (non-CAS and CAS groups) were performed using an independent sample t-test. Measurement data that did not conform to a normal distribution were presented using the median (interquartile range), with the group comparisons analyzed using the Mann–Whitney rank-sum test. The count data are presented as percentages (%), and the group comparisons were made using χ^2 tests or Fisher's exact test. Independent variables with p-values lower than 0.1 in the single-factor analysis were employed in the multivariate logistic regression analysis to determine the risk factors for CAS. A $P < 0.05$ was regarded as statistically significant.

3. Results

As shown in Table 1, there was no significant difference between the non-CAS and CAS groups in gender; history of drinking, hypertension and coronary heart disease; BMI values; levels of TC, HDL-C, LDL-C, uric acid; GFR and fibrinogen (all $P > 0.05$). However, there was a significant difference between the two groups in age, history of smoking, history of stroke, history of diabetes and the levels of TG,

Table 1
Comparison of the baseline demographics and clinical characteristics of the control group and carotid atherosclerosis (CAS) group.

Parameters	Control	CAS	*P*-value
Demographic			
Patients number	82	62	–
Age, year	62.35 ± 8.20	71.02 ± 8.80	< 0.01
Male sex	44 (54%)	29 (47%)	0.345
BMI, kg m^{-2}	25.70 ± 3.12	25.84 ± 3.62	0.689
Medical history			
Coronary heart disease	16 (17%)	15 (24%)	0.245
Stroke	8 (10%)	15(24%)	< 0.05
Diabetes	14 (17%)	24(39%)	< 0.01
Hypertension	55 (79%)	53(85%)	0.301
Smoking	21 (26%)	26 (42%)	< 0.05
Drink	17 (21%)	14 (23%)	0.558
Blood and Urine test			
TG, mmol/L	1.36 (0.99–1.98)	2.05 (1.11–2.76)	< 0.01
TC, mmol/L	4.98 (4.27–5.54)	5.10 (4.31–5.72)	0.373
LDL, mmol/L	3.08 (2.61–3.55)	3.28 (2.68–3.78)	0.221
HDL, mmol/L	1.29 (1.08–1.46)	1.21 (1.08–1.34)	0.120
FBG, mmol/L	5.88 ± 1.21	7.60 ± 1.99	< 0.01
Uric acid, umol/L	325.13 ± 82.96	355.73 ± 99.77	0.053
hs-CRP, mg/L	1.55 (0.88–3.36)	3.45 (1.48–4.93)	< 0.01
HCY, mmol/L	11.85 (10.00–15.88)	16.30 (11.1–22.93)	< 0.01
GFR,ml/min	82.98 ± 16.38	80.32 ± 16.02	0.343
Fibrinogen, g/L	2.76 ± 0.67	2.78 ± 0.55	0.819
Urine protein	12 (15%)	21(34%)	< 0.01

Note: Data presented as number (%) or median (first and third quartiles) or mean ± SD (for these with normal distribution). BMI: body mass index, TG: triglyceride, TC: total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FBG: fasting blood glucose, hs-CRP: high-sensitivity C-reactive protein, HCY: homocysteine, GFR: glomerular filtration rate.

FBG, hs-CRP, HCY and urine protein ($P < 0.01$ or 0.05).

Table 2 shows the 24 h ambulatory BPV metrics from both the non-CAS and CAS groups. There were significant differences between the two groups in the average daytime SBP, night SBP, 24 h SBP, daytime SSD, daytime DSD, 24 h SSD, 24 h DSD, 24 h dSBP and the percentage of patients with BP circadian rhythm (all $p < 0.05$).

Table 3 shows the results from the multivariate logistic regression analysis, demonstrating that age, smoking history, FBG, and daytime SSD were significant risk factors for the appearance of CAS in patients with essential hypertension ($P < 0.01$ or 0.05). In addition, dSBP was a protect factor.

Table 2
Comparison of the blood pressure variability (BPV) data of the control group and carotid atherosclerosis (CAS) group.

Metrics	Control	CAS	*P*-value
SBP			
SBP in daytime, mmHg	151.41 ± 9.10	154.60 ± 9.43	< 0.05
SBP in night, mmHg	132.56 ± 10.91	140.68 ± 9.48	< 0.01
SBP in 24 h, mmHg	142.48 ± 8.64	147.66 ± 8.26	< 0.01
SSD in daytime, mmHg	12.11 ± 2.10	14.63 ± 2.71	< 0.01
SSD in night, mmHg	9.40 ± 1.70	10.03 ± 2.06	0.050
SSD in 24 h, mmHg	12.73 ± 2.13	15.53 ± 2.91	< 0.01
dSBP in 24 h, mmHg	16 (13–27)	14 (12–16.25)	< 0.05
DBP			
DBP in daytime, mmHg	87.00 ± 5.37	88.44 ± 5.89	0.135
DBP in night, mmHg	78.59 ± 6.48	80.61 ± 5.35	0.124
DBP in 24 h, mmHg	82.74 ± 5.47	84.45 ± 5.07	0.102
DSD in daytime, mmHg	8.89 ± 1.97	10.05 ± 2.29	< 0.01
DSD in night, mmHg	6.77 ± 2.22	7.23 ± 1.83	0.178
DSD in 24 h, mmHg	9.72 ± 1.93.	11.33 ± 2.60	< 0.01
dDBP in 24 h, mmHg	8 (6.75–10)	8 (7–10)	0.905
BP circadian rhythm	32(39%)	11 (18%)	< 0.05
MBPS	21 (26%)	23 (37%)	0.126

Note: Data presented as number (%) or median (first and third quartiles) or mean ± SD (for these with normal distribution). SBP: systolic blood pressure, SSD: standard deviation of SBP, DBP: diastolic blood pressure, DSD: standard deviation of DBP, dSBP: difference between daytime SBP and nighttime SBP, dDBP: difference between daytime DBP and nighttime DBP, MBPS: morning blood pressure surge.

4. Discussion

BPV has recently attracted great attention in basic and clinical research. An increasing number of studies have concluded that increased BPV, independent of the average BP values, is a risk factor for cardiovascular and cerebrovascular diseases, which is more valuable than average BP to predict target organ lesions in hypertensive patients [9,10]. However, other studies reported that BPV was not relevant to target organ damage in hypertensive patients [18,19]. Therefore, further investigation on the role of BPV in cardiovascular and cerebrovascular diseases and target organ damage is of great significance.

It has been widely accepted that hypertension is a risk factor for cardiovascular diseases, and BP is independently associated with AS. High BP elevates flow shear stress, causing severe damage to artery walls and leading to arterial intimal thickening, plaque formation, and plaque instability. Based on 24 h ambulatory BP measurements, several studies have reported that both visit-to-visit BPV and short-term BPV were correlated with AS [10,11,13–15]. BPV has been reported to be closely associated with CAS [13–15,20]. However, due to the existence of various BPV indices and poor reproducibility of these indices, it is difficult to draw solid conclusions about the relationship between BPV and CAS. García et al. reported that there was a correlation between IMT and the SD of the DBP in awake time after adjustment [21]. However, Mancia et al. reported that the association between 24 h BPV (parameters of CV and SD) and carotid IMT disappeared after adjustment for confounding factors [22].

Various short-term BPV-related metrics, such as 24 h SSD and 24 h DSD, can be detected using 24 h ambulatory BP monitoring measurement. This method has been commonly used to clarify the relationship between BPV indices and BP, target organ damage, or other risk factors for cardiovascular disease [9–11]. However, there is no consensus on the normal range of the SD and coefficient of variation of BP in specific populations, as well as on how the BPV index changes in hypertension patients with different degrees of target organ damage.

In the current study, the univariate analysis revealed that the average daytime SBP, night SBP and daytime SSD, daytime DSD, 24 h SSD, and 24 h DSD in essential hypertension patients with CAS were higher than those with normal IMT. With a further multivariate logistic regression analysis, only the daytime SSD was shown to be independently associated with CAS in essential hypertension patients. This was in agreement with a study by Tatasciore et al. [13], where it showed that the IMT progressively increased daytime SSD for hypertensive population, and that the daytime SSD was an independent predictor of IMT in hypertensive subjects.

Our study also showed that dSBP was a protect factor for CAS in hypertensive patients. Previous studies have reported that the majority of BPV indices, including the pulse pressure, coefficient of variation independent of mean BP, 24-h maximum and minimum BP difference, were all positively correlated with the BP level and the severity of target organ damage [11]. Our results suggested that the decrease of dSBP may be acted as a new indicator for target organ damage. The possible reason is that, with the carotid baroreflex regulation of reflex function decreasing, the average nighttime BP levels increases, leading to a smaller dSBP.

The study demonstrated that age, smoking and FPF were positively correlated with CAS, which was consistent with some of the relevant literatures [23–25]. As mentioned above, there is no uniform standard of the normal SD or coefficient of variation of BP obtained from 24 h ambulatory BP monitoring in different populations. Bilo et al. [26] analyzed 24 h ambulatory BP monitoring data on 3863 Italian and Polish patients and found that the 24 h SSD and 24 h DSD were 13.8 ± 3.7 and 10.7 ± 2.5 mmHg, respectively. Tatasciore et al. [13] analyzed

Table 3
Results of multivariate logistic regression analysis for determining the risk factors for carotid atherosclerosis (CAS) in the hypertension patients.

Independent variable	Regression coefficient	SEM	Wald value	*p*-value	OR value	95% *CI*
Age	0.094	0.031	9.3122	0.002	1.098	1.034–1.167
Smoking	1.406	0.521	7.255	0.007	4.072	1.466–11.310
FBG	0.708	0.187	14.329	0.000	2.029	1.407–2.928
SSD in daytime	0.462	0.125	13.604	0.000	1.587	1.242–2.028
dSBP in 24 h	−0.090	0.034	7.057	0.008	0.914	0.855–0.977

Note: SEM: structural equation model, OR=odds ratio, CI=confidence interval, FBG: fasting blood glucose, SSD: standard deviation of SBP, dSBP: difference between daytime SBP and nighttime SBP.

24 h ambulatory BP monitoring data on 180 hypertensive patients and reported the corresponding values of 13.0 ± 4.1 and 10.9 ± 4.0 mmHg, respectively. Another study from Tatasciore's group reported that the daytime SSD from patients with newly diagnosed hypertension was 12.9 ± 4.1 mmHg, whereas it was 10.8 ± 3.8 mmHg for daytime DSD [27]. The findings of the present study were consistent with those of the aforementioned studies. As the sample size of patients, geographical difference, and times of BP measurement may affect the BPV results, it is difficult to unify the results. Future large-scale, multicenter studies are needed to explore the influence of different levels of BP on the degree of target organ damage.

Due to the relatively small sample size in the present study, selection bias is inevitable, making it difficult to draw any definitive conclusion. Nevertheless, this research is of clinical significance because it suggested that: 1) BPV had the potential to become a prospective evaluation index for CAS in hypertensive patients; 2) both the increase and decrease of BPV are likely to be abnormal.

In the future, there is a need to study more indicators to explore the relationship between the reduction of BPV and target organ damage. To treat hypertension, prevent the progression of atherosclerosis, and reduce the risk of damage to various target organs, it is reasonable to focus on reducing both BPV and average BP values rather than only on reducing average BP values. Future studies are also needed to explore the use of BPV as an alternative indicator for atherosclerotic disease, cardiovascular disease, and all-cause mortality. Therefore, during the treatment of hypertension, especially for hypertensive patients with CAS, the impact of antihypertensive drugs on BPV should be concerned. For instance, calcium channel blockers, thiazide diuretics can improve BPV at different levels. The effect of angiotensin converting enzyme inhibitors, angiotensin receptor blockers on BPV is inconsistent, and β-blockers could increase BPV [28–31]. The latest guidelines from the European Society of Hypertension (2013) and National Institute for Health Care and Excellence (2013) acknowledge the importance of BPV in hypertension [32]. However, BPV has not been included in the diagnostic criteria and risk stratification of hypertension, and the guidelines for the management of hypertension have largely ignored the role of BPV during the selection of antihypertensive therapy [33]. Investigating the significance of BPV in individualized treatment in hypertensive patients is therefore a key point in future research. To achieve that, the relationship between BPV and complications of hypertension (such as CAS) should be scientifically explored.

Conflict of interest statement

The authors declare no conflict of interest.

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