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Blood pressure variability estimated by average real variability predicts stroke in progression of acute ischemic stroke.

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Abstract

Background: The relationship between blood pressure variability and stroke in progression (SIP) in acute ischemic stroke (AIS) or transient ischemic attack (TIA) is still controversial. The aim of this study was to evaluate the impact of blood pressure variability estimated by average real variability on SIP.
Method: We prospected enrolled 251 consecutive patients with AIS or TIA (within 7 days after onset). Blood pressure was measured at 2 h intervals throughout the first 24 h, then every 4 h up to the 7th day. Average real variability was used to represent blood pressure variability. Ischemic stroke (IS) patients with an increase of national institutes of health stroke scale ≥ 3 scores or TIA patients in the event of stroke within 7 days after admission were defined as stroke. Patients were grouped in low and high blood pressure average real variability groups.
Results: The incidence rate of SIP was 8.3%. In univariate analysis, high D2-7 systolic blood pressure average real variability, female, and high total cholesterol level were significantly associated with SIP. In multivariate logistic regression analysis, SIP was independently predicted by total cholesterol and high D2-7 systolic blood pressure average real variability.
Conclusion: High D2-7 systolic blood pressure average real variability was an independent predictor of SIP in AIS or TIA patients.

Keywords: Stroke in progression, Ischemic stroke, Transient ischemic attack, Blood pressure variability, Average real variability.

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Introduction

Neurological deterioration that occurs within the first few hours or days after stroke onset has been defined as stroke in progression (SIP). It is reported that 4.5% -37% of patients with acute stroke develop SIP [1-5] increased the risk of morbidity and mortality. Many researchers have investigated the causes of neurological deterioration in acute stroke patients, but the causes of neurological deterioration are still not fully defined. It's commonly observed that the blood pressure value on admission in patients admitted for ischemic stroke (IS) or transient ischemic attack (TIA) is highest and falls spontaneously in the subsequent hours or days [6-11].

Blood pressure variability (BPV)-the variation of blood pressure continuously with time is presumed to be a strong and independent predictor of stroke in general [12-14], potentially more powerful than the absolute blood pressure levels [15]. However, previous studies mostly shed light on the association between outcome and long-term BPV [16-18], but the predictive value of short-term BPV remains unclear, particularly BPV during the acute phase of IS [19]. In addition, previous studies mostly were designed to observe the prognosis of BPV for hypertensive patients, previous stroke or TIA patients [16-18], not for acute ischemic stroke (AIS) or TIA patients. Furthermore, various indexes, such as standard deviation (SD), coefficient of variation (CV), variation independent of mean (VIM), weighted standard deviation (wSD), and average real variability (ARV), have been used to evaluate BPV in different researches, but uncertainty remains about which index to assess properly the value of BPV as a risk factor. The aim of this prospective study was to assess the predictive value of BPV estimated by ARV on SIP in AIS or TIA.

Materials and Methods

Participants and study setting

This was a prospective cohort study based on the clinical data of 251 patients admitted consecutively for IS or TIA within 7 days after onset to the Neurological Department, the First Affiliated Hospital, Jinan University Guangzhou, from August 2012 to August 2013. Cerebral computerized tomography (CT), or magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were performed and described

routinely within 24 h after admission. The diagnosis of TIA and IS was based on clinical symptoms and imaging tests according to standardized diagnostic criteria [20].

Inclusion criteria: Patients were chosen (1) whose cases conformed to the diagnostic criteria of the 2005 China cerebrovascular disease prevention and treatment guidelines for IS; (2) whose time of stroke onset was not more than 7 days prior to inclusion.

Exclusion criteria: Patients were excluded if they (1) were below 18 years of age; (2) had inadequate BP measurements; (3) had other serious or life-threatening disease before stroke onset; (4) received thrombolytic therapy; (5) previous stroke (modified Rankin Scale score, MRS>2). The research protocol was approved by the medical ethical committee of the First Affiliated Hospital, and inform consent was obtained from every patient.

Measurement of blood pressure

The casual supine blood pressure (BP) was measured in the non-paralyzed arm using a standard electronic sphygmomanometer (OMROM-HEM-7200) on admission. In the neurological intensive care unit, BP was measured at 2 h intervals during the first 24 h by using a noninvasive BP monitoring device (BeneView T5), and then every 4 h, up to the 7th day after admission by using standard electronic sphygmomanometer (OMROM-HEM-7200) by trained nurse, with 1 h error in the daytime and 2 h error in the nighttime. All BP records were entered manually into the electronic medical record (EMR) system. In addition, we used ARV, which weighted for the time interval between consecutive readings, to represent BPV [21]. It was calculated by the following formula:

$$ARV = |BP_{K+1} - BP_K|$$

(k ranges from 1 to n-1 and w is the time interval between BP_k and BP_{k+1}. n is the number of blood pressure readings).

The BPV during the first 24 h and the 2-7 days (D2-7) was described using systolic blood pressure average real variability (SBP-ARV) and diastolic blood pressure average real variability (DBP-ARV).

Stroke risk factors

Data on stroke risk factors were collected, including age, gender, history of hypertension (BP ≥ 140/90 mmHg according to the World Health Organization-International Society of Hypertension guidelines [22] or already under treatment with antihypertensive drugs), history of diabetes mellitus (fasting plasma glucose level ≥ 7.0 mmol/l, or plasma glucose ≥ 11.1 mmol/l two hours after a 75 g oral glucose load as in a glucose tolerance test, or symptoms of hyperglycemia and casual plasma glucose ≥ 11.1 mmol/l, or glycated hemoglobin (Hb A1C) ≥ 6.5% [23] or under hypoglycemic treatment), history of hyperlipidemia (total cholesterol concentration >6.22 mmol/L (240 mg/dL), or triglycerides >2.26 mmol/L, or HDL-cholesterol <1.14 mmol/L the day after admission or already under lipid lowering therapy for hyperlipidemia), history of symptomatic ischemic heart disease (proven myocardial infarction, history of angina or existence of multiple lesions on thallium heart isotope screen or evidence of coronary disease on coronary angiography), atrial fibrillation (documented during hospitalization or history of atrial fibrillation), current cigarette smoking, alcohol abuse (>50 g per week), or previous stroke.

Assessment of outcome

The neurological severity on admission and at 7 days (or at discharge if earlier) was assessed by the National Institutes of Health Stroke Scale (NIHSS) by trained stroke neurologists. The primary outcome of this study was SIP which was defined as an increase of ≥ 3 scores in the NIHSS during the first 7 days after admission for IS patients; and TIA patients during hospitalization in the event of stroke can be diagnosed as SIP.

Statistical analysis

Data were presented as mean ± SD, median (interquartile range [IQR] for continuous variable), or as the number (%) of subjects for categorical variables. Comparisons of baseline characteristics and BPV parameters between patients of the SIP and Non-SIP (NSIP) groups were conducted with Pearson χ^2 test, Mann-Whitney test, or Student t test according to the type of variable. In order to further examine the consistency of ARV in its impact on SIP by different levels. Patients were divided into low (≤ median) and high (>median) groups using the median value of systolic and diastolic ARV during the first 24 h and the 2-7 days. The proportions of patients with SIP were calculated in each group and the relationship between ARV and SIP was assessed using the Pearson χ^2 test. All parameters showing significance in the univariate analysis were tested in a multivariate logistic regression model to explore predictors for SIP. Due to the possible colinearity of tested variables, we applied a stepwise logistic regression model. All analysis were performed using the SPSS 19.0 software (SPSS inc, Chicago, IL, USA), and a probability value of $p<0.05$ was considered as statistically significant.

Results

Demographic characteristics and baseline data of patients

Two hundred and fifty one patients met the inclusion criteria. Forty seven patients who did not finish the follow up or lacked of enough data were excluded from the final analysis. Eventually, a total of 204 patients were determined to have enough data and were enrolled in this study. The demographic characteristics and baseline data of the patients were shown in Table 1.

Table 1. *Demographic characteristics and baseline data of 204 ischemic stroke or TIA patients.*

Variable	All patients

	(n=204)
Female	66 (32.4)
Age, year, mean ± SD	64.24 ± 12.86
Current smoker	67 (32.8)
Alcohol consumption	15 (7.4)
Previous stroke	51 (25.0)
Coronary artery disease	31 (15.2)
Dyslipidemia	16 (7.8)
Atrial fibrillation	18 (8.8)
Diabetes	53 (26.0)
Hypertension	125 (61.3)
Types of ischemic cerebrovascular disease	
TIA	28 (13.7)
IS	176 (86.3)
Antihypertensive treatment	25 (12.3)
Antiplatelet therapy	200 (98.0)
Lipid-lowing treatment	203 (99.5)
Baseline NIHSS, median (IQR)	4 (1,7)
Total cholesterol, mmol/L	4.98 ± 1.19
Triglyceride, mmol/L	1.73 ± 1.01
Low density lipoprotein cholesterol, mmol/L	3.03 ± 1.11
High density lipoprotein cholesterol, mmol/L	1.12 ± 0.22
Fasting blood glucose, mmol/L	6.74 ± 3.15
Glycosylated hemoglobin a1 c, mmol/L	6.62 ± 1.94
D dimer, mmol/L	742.52 ± 1138.01
Hypersensitivity c-reactive protein, mmol/L	11.19 ± 26.56
Admission blood pressure, mmHg	
SBP	156.68 ± 24.57
DBP	86.25 ± 15.48

Values are median and interquartile range (IQR) for NIHSS score and No. (%) or mean ± SD for other items. TIA: Transient Ischemic Attack; IS: Ischemic Stroke; NIHSS: National Institutes of Health Stroke Scale; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Comparison of baseline characteristics between patients of SIP and NSIP

We observed SIP in 17 (8.3%) patients. All of the patients were given standardized therapy according to the current guidelines. Two hundred patients (98.0%) were given anti-platelet therapy, two hundred and three patients (99.5%) were prescribed with statin therapy, and twenty five patients (12%) were given anti-hypertension therapy. In univariate analysis of the baseline and clinical data between the SIP and NSIP group patients showed that female and high total cholesterol level were associated with SIP (p=0.005) (Table 2).

Table 2. *Comparison of Baseline Characteristics between patients of SIP and NSIP groups.*

Parameter	NSIP (n=187; 91.7%)	SIP (n=17; 8.3%)	P value
Female	56 (30.0)	10 (59.0)	0.015
Age ≥ 60 years	115 (61.5)	13 (76.5)	0.222
Current smoker	64 (43.2)	3 (17.6)	0.163
Alcohol consumption	14 (7.5)	1 (5.9)	1.000
Previous stroke	45 (24.1)	6 (35.3)	0.465
Coronary artery disease	27 (14.4)	4 (23.5)	0.518
Dyslipidemia	16 (8.5)	0 (0)	0.432
Atrial fibrillation	17 (9.1)	1 (5.9)	1.000
Diabetes	47 (25.2)	6 (35.3)	0.531
Hypertension	114 (61.0)	11 (64.7)	0.762
Interval from onset to arrival ≤ 12 h	81 (43.3)	10 (58.8)	0.218
Types of ischemic cerebrovascular disease			0.177
TIA	28 (15.0)	0 (0)	
IS	159 (85.0)	17 (100.0)	
Antihypertensive treatment	24 (5.3)	1 (5.8)	0.652

Antiplatelet therapy	183 (98.0)	17 (100.0)	0.543
Lipid-lowing treatment	186 (99.5)	17 (100.0)	1.000
Age, y	63.63 ± 13.04	70.06 ± 12.68	0.052
Baseline NIHSS, median (IQR)	4 (1.0,7.0)	4 (0.5,7.5)	0.670
Admission blood pressure, mmHg			
SBP	156.05 ± 24.66	163.59 ± 23.06	0.227
DBP	85.98 ± 14.98	89.29 ± 20.52	0.524
Total cholesterol, mmol/L	4.89 ± 1.15	6.04 ± 1.05	0.000
Triglyceride, mmol/L	1.69 ± 1.00	2.11 ± 1.16	0.108
Low density lipoprotein cholesterol, mmol/L	2.98 ± 1.06	3.60 ± 1.48	0.111
High density lipoprotein cholesterol, mmol/L	1.12 ± 0.22	1.15 ± 0.22	0.647
Fasting blood glucose, mmol/L	6.55 ± 2.88	8.80 ± 4.94	0.081
Glycosylated hemoglobin a1 c, mmol/L	6.57 ± 1.86	7.30 ± 2.80	0.176
D dimer, mmol/L	729.66 ± 1130.85	890.81 ± 1249.69	0.600
Hypersensitivity c-reactive protein, mmol/L	11.37 ± 27.38	9.32 ± 16.10	0.770

Values are median and interquartile range (IQR) for NIHSS score and No. (%) or mean ± SD for other items. TIA: Transient Ischemic Attack; IS: Ischemic Stroke; NIHSS: National Institutes of Health Stroke Scale; SBP: Systolic Blood Pressure; and DBP: Diastolic Blood Pressure; NSIP: Non-Stroke In Progression; SIP: Stroke in Progression.

Comparisons of systolic and diastolic BPV parameters between NSIP and SIP

Comparisons of systolic and diastolic BPV parameters between NSIP and SIP group patients were presented in Table 3. The results showed that 24 h SBP ARV (p=0.034 Student's t-test) and D2-7 SBP-ARV (p=0.001 Student's t-test) were significantly higher in the SIP group than that in the NSIP group. In univariate analysis of systolic and diastolic BPV ARV, each of them were divided into low ARV group and high ARV group, and we found an association between high D2-7 SBP-ARV and SIP (p=0.005 Student's t-test) (Table 4).

Table 3. *Comparison of systolic and diastolic BPV ARV between SIP and NSIP groups.*

Parameters	NSIP (n=187; 91.7%)	SIP (n=17; 8.3%)	P-value
24 h SBP-ARV, mmHg*	11.13 ± 3.83	13.22 ± 4.33	0.034
24 h DBP-ARV, mmHg	8.19 ± 3.06	8.85 ± 3.04	0.394
D2-7 SBP-ARV , mmHg*	11.98 ± 3.73	15.41 ± 5.73	0.001
D2-7 DBP-ARV, mmHg	8.04 ± 2.46	9.53 ± 4.30	0.175

Values are mean ± SD. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ARV: Average Real Variability.

Table 4. *Univariate analysis of patients with high and low systolic and diastolic ARV between the SIP and NSIP groups.*

	NSIP (n=187)	SIP (n=17)	P-value
24 h SBP-ARV			
Low (≤ 10.96)	97 (51.9)	5 (29.4)	0.076
High (>10.96)	90 (48.1)	12 (70.6)	
24 h DBP-ARV			
Low (≤ 7.75)	97 (51.9)	6 (35.3)	0.291
High (>7.75)	90 (48.1)	11 (64.7)	
D2-7 SBP-ARV			
Low (≤ 11.82)	99 (53.0)	3 (17.6)	0.005
High (>11.82)	88 (47.0)	14 (82.4)	
D2-7 DBP-ARV			
Low (≥ 7.75)	95 (50.8)	8 (47.0)	0.768
High (>7.75)	92 (49.2)	9 (53.0)	

Values are No. (%). SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ARV: Average Real Variability.

Final stepwise logistic regression model to predict SIP

In a stepwise logistic regression model including all parameters showed a significant difference between the SIP and NSIP group. In univariate analysis (female, total cholesterol, D2-7 SBP-ARV), total cholesterol (odds ratio [OR]=2.32, 95% confidence interval [CI]=1.46-3.69, p=0.000), and D2-7 SBP-ARV (OR=5.96, 95% CI=1.56-22.78, p=0.009) remain independent predictors of SIP at day 7 (Table 5).

Table 5. *Final stepwise logistic regression model to predict SIP.*

Variable	Adjusted OR (95%CI)	P value
Total cholesterol	2.32 (1.46, 3.69)	0.000
High D2-7 SBP-ARV	5.96 (1.56, 22.78)	0.009

SBP: Systolic Blood Pressure; ARV: Average Real Variability.

Discussion

The main findings of this study were that systolic BPV estimated as ARV during the acute phase of IS/TIA was independently associated with SIP. Previous studies mostly enrolled blood pressure patients and their results are the reflection of association between BPV and secondary or primary stroke prevention [24-26]. Currently, there are few prospective studies [9,27,28] had focused on the relationship between BPV and SIP. Ishituska et al. [29] had found that patients with average SBP ≥ 166 mmHg had higher rate of SIP compared with patients with average SBP ≤ 132 mmHg. The Glycine Antagonist in Neuroprotection International Trial also found that increased weighted average Mean Arterial Pressure (MAP) was the independent predictor of SIP within 7 days, every weighted average MAP increased 10 mmHg, and the rate of SIP increased 15% [28]. Meanwhile, U shape association was found between average SBP (24 h) and SIP [9]. A recent retrospective study enrolled 1161 patients found that all variability parameters were linearly associated with early neurological deterioration independent of mean BP and potential clinical variables, which is similar to our study [2]. The mechanism underlying the relationship between BPV and SIP has not been clarified. We can only speculate about the mechanisms underlying this finding, in subjects with stiff arteries, when systolic blood pressure increases, often diastolic blood pressure increases less or even falls, giving rise to larger variability [30]. During the acute phase of stroke, cerebral auto regulation is impaired and blood flow becomes completely dependent on systemic BP. Increased arterial stiffness could also promote excessive flow pulsatility into small vascular beds. This haemodynamic stress, pulsatile pressure or BP variability can cause a 'tsunami effect' towards cerebral parenchyma [31]. For this reason, fluctuations in BP may be detrimental for ischemic territories, particularly in the presence of an anatomic or functional compromise of small cerebral vessels [30,32]. For this concern, the three most recently systematic review and meta-analysis also had proved this theory [33-35].

This prospected study was different from others by a more intense blood pressure monitoring during the initial 7 days of AIS. Although previous retrospective studies showed that early blood pressure changes were related to SIP [9,28,29], these studies monitored blood pressure at much less time points than this study, Shitsuka et al. [29] at 7 time points (on admission, 10 am, 14 pm, 18 pm in the next 2 days) and Castillo et al. [9] at 6 time points (every 4 h in the first 24 h after admission), Aslanyan et al. [28] at 7 time points. In this study, blood pressure was monitored in a much more intense pattern, which is 54 time points (every 2 h in first 24 h then followed by every 4 h in the next 7 days). We had continuously collected more blood pressure data in a longer time and it gave us a better chance to reflect the true BPV during the admission time. The reading to reading BPV was more accurate by acquiring more blood pressure data in this study. Furthermore, previous studies were predominantly retrospective researches, which were designed to investigate the prognosis of long-term BPV for hypertensive, previous stroke or TIA patients [15-18]. Very seldom studies had been designed to prospectively explore the relationship between SIP and short term BPV. This study was a prospected study, only focused on the subjects of AIS or TIA patients.

At last, we adopted the ARV as the main index of BPV in the present study. Proper selection of the variability index is critical to assessing the value of BPV as a risk factor [21]. There are some defects among them and may not reflect the BPV truthfully and properly, SD and CV ignore the order of blood pressure data; as a result, two subjects with different clinical meaning may have the same SD or CV, wSD ignore the adverse effect of nocturnal decreases in blood pressure, VIM is a statistical tool which calculated complexly and not suitable for clinical application. Compared with them, ARV is an emerging index to represent BPV and it has many merits. First, it takes more consideration of the time series nature of blood pressure values so that may reflect individual BPV more accurately. In addition, it can reflect the correlation between BPV and target organs more reliably to be used for establishing the prognostic significance of BPV. Furthermore, its formula shows simple, easy to be calculated, simple to be used in clinical practice.

Several limitations of this study should be noted. Firstly, this is a single-center study, and the results may have limitation on generalization. Secondly, we didn't measure the potential influence of sub-type of stroke, or the extra and intra cranial artery stenosis which may partly explain the findings. Thirdly, the initial NIHSS score of this cohort was low (NIHSS=4). So our findings may not represent all type of ischemic stroke and only applied in particular to patients with mild stroke. Fourthly, there are nearly 20% of the patients were enrolled to this study at the time of 72 h after onset. For this reason, SIP rate of this study maybe under detected. At last, due to the reasons of limited sample size, BPV ARV was only divided as two groups. If categorize the BPV ARV with more levels, we may have the opportunity to find a linear relationship between increased ARV and SIP rate. Despite of the above limitations, our results suggested that high systolic BPV during the acute phase of IS/TIA may be an independent risk factor for SIP within the initial 7 days after admission, particularly for the patients with mild stroke. This implies that BPV estimated by ARV could be potentially modifiable risk factor for the development of SIP. Further prospected studies with larger sample size are warranted.

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