

Average Real Variability of Diastolic Blood Pressure During Acute Phase Could Independently Predict 3-month Functional Outcome for Ischemic Stroke

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Abstract: *Background and purpose*—Blood pressure variability has a significant effect on stroke. There were controversial reports about its relationship with short term functional outcome remains controversial for ischemic stroke or transient ischemic attack (TIA). There were limited studies about its long-term effect. Our aim was to elucidate the effect of BPV on a 3-month functional outcome in patients with acute ischemic stroke or TIA. *Methods*—In this prospective observational study, a consecutive series of 400 patients were enrolled with acute ischemic stroke or TIA within 7 days. All patients were referred and monitored for BP at 2-hour intervals in the first 24 hours. Afterward, the BP was recorded every four hours up to the 7th day, with 1-hour deviation the daytime and 2 hours at night. All BP results were recorded into an electronic medical record (EMR) system. Average real variability (ARV) was used to analyze the blood pressure variability (BPV). All patients were followed up as planned for 90 days. The primary outcome was evaluated by the modified Rankin Scale (mRS); an unfavorable outcome was mRS \geq 2. For comparison, patients were respectively divided into two groups based on systolic blood pressure ARV (SBP ARV) or diastolic blood pressure ARV (DBP ARV). A multivariate logistic regression model was used to estimate the effect of between ARV BPV on functional outcomes. *Results*—Among the 400 patients, 46 (11.4%) had an unfavorable outcome (mRS \geq 2) at 90 days. Their mean 24h DBP ARV was significantly higher than others (10.42 \pm 3.63 vs. 9.83 \pm 4.27 mm Hg; $p=0.03$). The high 24hDBPARV was defined above the median of 7.75 mmHg, which was statistically associated with an unfavorable outcome (64.7% vs. 35.3%; $P=0.004$). Further stepwise logistic regression analysis indicated that 24h high DBPARV was the independent predictor of an unfavorable outcome (adjusted OR 2.44%, 95% confidence interval: 1.24-4.74, $P<0.01$). *Conclusions*—High DBPARV during the acute phase is an independent and significant predictor of 90-day functional outcome for ischemic stroke or TIA.

Keywords: Blood Pressure in Acute Stroke, Ischemic Stroke, Transient Ischemic Attack, Acute Stroke Outcome

1. Introduction

Blood pressure variation (BPV) – the variation of blood pressure continuously with time [1-3] has been proposed as a reliable and independent predictor of the long-term risk of stroke, which was more specific for prediction than simple blood pressure levels [4]. The clinical significance of BPV is uncertain during the acute phase of the stroke. A recent

systematic review of seven studies suggested that systolic BPV was significantly associated with poor functional outcomes (pooled odds ratio per 10mm Hg increment, 1.2; 95% confidence interval: 1.1-1.3) [5]. More prospective studies were required to investigate how best to measure and define the BPV standard in acute stroke, as well as to determine its prognostic significance [5]. Various mathematical indexes were used to evaluate BPV in

different reports, such as standard deviation (SD), coefficient of variation (CV), variation independent of the mean (VIM), weighted standard deviation (wSD), and average real variability (ARV). But It's also uncertain for variability index calculation to precisely demonstrate the BPV significance for the prognostic prediction. This observational study was conducted to investigate the correlation between the BPARV and the short-term functional outcome in patients with acute ischemic stroke or transient ischemic attack (TIA).

2. Methods

2.1. Subjects and Setting

This was a prospective observational study, including 451 patients with ischemic stroke or TIA within 7 days after onset. They were admitted to the Department of Neurology, the First Affiliated Hospital, Jinan University, Guangzhou, China, from August 2012 to August 2013. All patients were monitored in the neurological intensive care unit (NICU) in the first 24 hours after admission. Afterward, patients were transferred out NICU according to its performance and clinical diagnosis. Cranial computerized tomography (CT) or magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were performed routinely within 24 hours after admission. TIA and ischemic stroke were diagnosed according to standardized diagnostic criteria [6]. This study excluded cases with thrombolysis, inadequate BP measurements, other life-threatening comorbidities before stroke onset, or modified Rankin Scale score (mRS) >2 caused by a previous stroke. The research protocol was approved by the medical ethical committee of the First Affiliated Hospital, Jinan University, for clinical research, and informed consent was obtained from all participants.

2.2. Measurement of Blood Pressure

Casual supine blood pressure (BP) was measured in the non-paralyzed arm using a standard electronic sphygmomanometer (OMROM-HEM-7200) and the appropriate cuff size on admission. BP was measured at 2-hour intervals throughout the first 24 hours using a noninvasive BP monitoring device (Bene View T5) in NICU, and then every 4 hours, up to the 7th day in general ward after admission, using a standard electronic sphygmomanometer (OMROM-HEM-7200) by trained nurses, with 1-hour deviation in the day and 2 hours at night. All BP results were recorded into the electronic medical record (EMR) system. The BP profile during the first 24 hours (h) and the 2-7 days (D_{2-7}) was described using various parameters for each of systolic blood pressure (SBP) and diastolic blood pressure (DBP): SD, CV. As an index of short term BPV, average real variability (ARV) [7] was used for evaluation, which was weighted for the time interval between consecutive readings. It was calculated by the following formula:

$$ARV = \frac{1}{N-1} \sum_{k=1}^{n-1} w \times |BP_{k+1} - BP_k|,$$

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.

2.3. Stroke Risk Factors

The prognostic functional outcome at 90 days and the baseline National Institute of Health stroke scale (NIHSS) score were collected as planned. Other general personal characteristics were also recorded, including age, gender, hypertension ($BP \geq 140/90$ mmHg [8] or antihypertensive treatment), diabetes mellitus, hyperlipidemia, symptomatic ischemic heart disease (myocardial infarction, angina or existence of multiple lesions on thallium heart isotope screen or coronary disease), atrial fibrillation, current cigarette smoking, alcohol abuse (>50 g per week), and stroke history.

2.4. Assessment of the Clinical Outcome

Two trained stroke neurologists were blinded and respectively arranged to assess functional outcome at 90 days. The functional outcome was assessed by the mRS score at 90 ± 7 days after the treatment. It was dichotomized into a favorable outcome (mRS 0 to 1) or unfavorable outcome (mRS 2 to 6, death was graded 6). On admission (1st day) and on the 90th day, the modified ranking scale was evaluated.

2.5. Statistical Analysis

All analysis was performed using SPSS for Windows, release 19.0 (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered as statistically significant. Quantitative variables were summarized as mean \pm SD, categorical variables as frequency distribution. Comparisons of baseline characteristics or BPV parameters for predicting functional outcome were conducted with the Pearson χ^2 test, Mann-Whitney U test, or Student *t*-test as described. For ARV analysis, patients were divided into low (\leq median) and high ($>$ median) groups using the median value of systolic and diastolic ARV during the first 24 hours and over the subsequent 2-7 days. The patient proportion with the unfavorable outcome was calculated and its correlation with ARV was assessed using a Pearson χ^2 test. All parameters with statistical significance ($p < 0.05$) in the univariate analysis were introduced into a multivariate logistic regression model to explore predictors for unfavorable functional outcome. Due to the possible collinearity of tested variables, a stepwise logistic regression model was used.

3. Results

451 patients were initially enrolled with ischemic stroke or TIA. Fifty-one patients were excluded without the follow-up response. For the final 400 patients from 2012-2013, the median age was 64.3 ± 10.3 (range 34-93) years, and 123 patients were female. At admission, 372 patients (93%) were diagnosed with ischemic stroke, and 28 patients (7%) had TIA. A history of hypertension was present in 247 (61.8%)

patients. Most patients did not know their typical blood pressure values. 58.1% were under antihypertensive therapy. All patients were given standardized therapy according to the guidelines. Forty-four patients (11%) were given anti-hypertension therapy, 386 patients (96.5%) antiplatelet therapy, and 385 patients (96.2%) were prescribed with statin

therapy. Among them, 208 cases were minor stroke (NIHSS<4). Demographic data and clinical characteristics of 400 patients were presented in Table 1. Admission within 12 hours after onset was significantly associated with better functional outcome ($P=0.018$).

Table 1. Comparison of clinical data between the favorable and unfavorable outcomes groups patients.

Patient characteristics	Favorable outcomes (mRS 0-2) (n=354)	Unfavorable outcomes (mRS 3-5) (n=46)	P value
Female (%)	108 (30.5%)	15 (32.6%)	0.772
Age (years)	63.5±13.0	65.2±14.3	0.429
Current smoker (%)	119 (33.6%)	14 (30.4%)	0.667
Alcohol consumption (%)	28 (7.9%)	3 (6.5%)	0.853
Previous stroke (%)	76 (21.4%)	9 (19.6%)	0.767
Coronary artery disease (%)	43 (12.1%)	6 (13.0%)	0.861
Hyperlipidemia (%)	18 (5.0%)	4 (8.7%)	0.505
Atrial fibrillation (%)	23 (6.5%)	5 (10.9%)	0.274
Diabetes mellitus (%)	90 (25.4%)	8 (17.4%)	0.233
History of hypertension (%)	223 (62.9%)	24 (52.2%)	0.148
Interval time for onset to admission≤12 hours (%)	162 (45.8%)	12 (26.1%)	0.018
TIA (%)	28 (7.9%)	0 (0%)	0.048
Antihypertension therapy (%)	40 (11.3%)	4 (5.8%)	0.595
Antiplatelet therapy (%)	343 (98.0%)	43 (93.4%)	0.383
Statin therapy (%)	340 (96.0%)	45 (97.8%)	0.416
NIHSS at admission, Median (IQR)	3 (1,7)	1 (1,1)	0.137
Blood pressure at admission (mmHg)			
SBP	155.2±24.7	153.8±24.0	0.710
DBP	86.7±15.8	86.5±20.7	0.948
TC* (mmol/L)	4.9±1.2	5.7±4.6	0.299
TG (mmol/L)	1.8±1.2	1.7±1.2	0.540
LDL-C (mmol/L)	3.1±1.5	2.9±1.0	0.589
HDL-C (mmol/L)	1.2±0.7	1.2±0.3	0.579
FBG (mmol/L)	6.7±3.0	6.2±2.2	0.320
HbA1c	6.5±1.9	6.3±1.5	0.554
D-D	1216.3±1934.2	1278.6±1639.8	0.840
hs-CRP (mg/L)	14.5±37.8	12.5±26.3	0.745

Comparisons of systolic and diastolic BPV parameters between favorable and unfavorable outcome patients were presented in Table 2. Unfavorable results were significantly associated with higher 24h DBP ARV ($P=0.03$). For the univariate analysis of systolic or diastolic ARV, patients were respectively divided into groups with low and high ARV. The

significant association was demonstrated between high 24hDBP-ARV and unfavorable functional outcome ($P=0.005$) (Table 3). After adjusting the known baseline predictors, 24h DBP ARV, and admission within 12 hours after onset were associated with favorable outcome at day 90 (Table 4).

Table 2. Comparison of Systolic and Diastolic BPV Parameters between the favorable and unfavorable outcome groups patients.

	Favorable outcomes (n=354)	Unfavorable outcomes (n=46)	P Value
24h SBP-SD (mmHg)*	13.1±5.3	12.9±5.6	0.826
24h SBP-CV*	0.1±0.0	0.1±0.0	0.997
24h SBP-ARV (mmHg)*	11.2±4.6	10.5±4.1	0.300
24h DBP-SD (mmHg)	10.8±5.3	11.8±5.6	0.269
24h DBP-CV	0.2±0.1	0.2±0.1	0.377
24h DBP-ARV (mmHg)	9.8±4.3	10.4±3.6	0.030
D ₂₋₇ SBP-SD (mmHg)*	12.8±4.7	13.0±4.3	0.778
D ₂₋₇ SBP-CV*	0.1±0.0	0.1±0.0	0.726
D ₂₋₇ SBP-ARV (mmHg)*	12.0±4.6	12.4±4.0	0.579
D ₂₋₇ DBP-SD (mmHg)*	8.2±3.1	8.7±2.9	0.288
D ₂₋₇ DBP-CV	0.1±0.0	0.1±0.0	0.356
D ₂₋₇ DBP-ARV (mmHg)	8.1±3.2	8.5±2.6	0.433

Values are mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, coefficient of variation; ARV, average real variability.

Table 3. Univariate analysis of patients with high and low systolic and diastolic ARV between patients of favorable and unfavorable outcomes groups.

	Favorable outcomes (n=354)	Unfavorable outcomes (n=46)	P Value
24h SBP-ARV			0.555
Low (≤ 11.0)	176 (49.7)	25 (54.3)	
High (> 11.0)	178 (50.3)	21 (45.7)	
24h DBP-ARV			0.004
Low (≤ 7.8)	187 (52.8)	13 (28.2)	
High (> 7.8)	167 (47.2)	33 (71.7)	
D ₂₋₇ SBP-ARV*			0.531
Low (≤ 11.8)	175 (49.4)	25 (54.3)	
High (> 11.8)	179 (50.6)	21 (45.7)	
D ₂₋₇ DBP-ARV			0.508
Low (≥ 7.8)	180 (50.8)	21 (45.7)	
High (> 7.8)	174 (49.2)	25 (54.3)	

Table 4. Final stepwise logistic regression model to predict unfavorable outcomes.

Variable	Adjusted OR (95%CI)	PValue
Interval time <12hours	0.45 (0.23, 0.91)	0.009
24h high DBP-ARV	2.43 (1.24, 4.74)	0.001

SBP, systolic blood pressure; ARV, average real variability.

(Final stepwise logistic regression model to predict poor outcome at 90 days, included variables: interval time from onset to admission, and 24hours DBP-ARV).

4. Discussion

Blood pressure variability might significantly predict the prognostic outcome of clinical stroke. In previous studies [11-16], BP monitoring was recommended at the early stage of stroke. In acute ischemic stroke, dramatic short-term change in BP might significantly influence the patients' clinical performance and follow-up outcome. Previous reports [17-20] showed that BPV could effectively predict the long-term functional outcome, and SBPV was independently associated with a long-term unfavorable functional outcome [11-16, 21-23]. There was a limited prospective study about the clinical significance of BPV in the short-term functional outcome in the acute stage of ischemic stroke.

Our research protocol was designed to investigate the BPV prediction for acute functional outcomes. As expected, higher DBP ARV in the first 24 hours was found as the predictor for a 3-month unfavorable functional outcome. As reported, there were only 8 studies about the association between DBPV and stroke outcome [23]. Among them, only one study confirmed DBPV was related to the outcome at 30 days [24]. But these studies enrolled patients with intracerebral hemorrhage and ischemic stroke simultaneously, and results were biased due to the mixed sample. More importantly, varied BPV parameters were used to analyze different outcomes [5]. Instead, we solely collected ischemic stroke patients and introduced one unique parameter, ARV BPV, to discuss the clinical correlation between DBPV and outcome at 90 days. Currently, there was no consensus parameter to estimate BPV. Various indexes were applied in previous studies, including SD squared differences, CV, wSD, variation independent of mean (transformation of SD uncorrelated with mean), and so on. The effects of DBPV

indices on outcome were considered in 16 studies. SD DBP was the most frequent parameter [5]. For accurate BPV assessment, SD and CV ignore the data order of BP, and two sets with different clinical meanings might have the same SD or CV. wSD ignores the adverse effect of nocturnal decreases in BP, while VIM is not suitable for clinical application⁷. ARV included more information about data variance and its sequence order. ARV adequately takes consideration of the sequential effect of BP monitoring instead of simple value variance. It might reflect the individual's BPV more accurately. ARV is also reliable and straightforward to be calculated and easy for clinical practice.

In our results, the mean 24h DBP ARV at baseline was significantly higher among patients with an unfavorable outcome than others at 90 days (10.42 ± 3.63 vs. 9.83 ± 4.27 mm Hg; $p=0.03$). The high 24hDBPARV, above the median of 7.75 mmHg, was definitely associated with an unfavorable outcome (64.7% vs. 35.3%; $P=0.004$). Further stepwise logistic regression analysis showed that 24h high DBPARV was the strong and independent predictor of an unfavorable outcome (adjusted OR 2.44%, 95% confidence interval: 1.24-4.74, $P<0.01$).

The detailed mechanism for our finding was unknown. Normally, systolic and diastolic BP will parallel change under physiological stimulation. This paralleling correlation might be altered due to stiff arteries [25-26]. SBP increases, but DBP increases less or even decrease, which could cause a more substantial variability. The pathophysiological effects of more extensive DBPVon brain tissue might vary based on the impairment degree in cerebral auto-regulation, which is influenced by infarct size and potentially salvageable penumbral tissue [27-28]. Perhaps in the initial period after onset, the potentially salvageable penumbral tissue was particularly vulnerable to BP fluctuation, where acute BP declines, especially DBP, increased the ischemia risk and reduced the reperfusion opportunity. This also explained why there was no significance between DBPV after 12 hours and short-term functional outcome in this study. This speculated mechanism also was referred to us by other large-scale studies, such as ECASSI and ECASSII [16]. The ECASSI study showed that DBPV decreases within 3 days after admission was independently related to a better functional outcome. In the ECASSII study [16], DBPV within 24 hours after admission was related to less hemorrhagic transformation and better functional outcomes.

There were very seldom prospective studies that applied one variability parameter as a clinical predictor for the stroke functional outcome [14]. Our DBP ARV result might significantly affect clinical practice for treating ischemic stroke or TIA patients. Our study still had limitations and need further verification. The large cohort study in multiple centers should be performed instead of our single hospital. Instead of minor stroke cases, more severe patients should be recruited to explore the clinical significance of DBP ARV in the stroke population. With the increasing cohort, the stratification analysis was applied to verify the clinical correlation between short-term functional outcomes of minor ischemic strokes to the BPV. The potential mechanism should also be studied biologically and clinically.

5. Conclusion

Our research implied that increased DBP ARV within the first 24 hours had impacts on functional recovery in acute ischemic stroke or TIA patients. These findings demonstrated the importance of BP monitoring and BP controlling in the acute phase of ischemic stroke. Further large scale multicenter prospected studies were required to verify our findings and explore the possible underlying mechanism.

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