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Blood pressure variability related to early outcome of acute ischemia stroke in a prospective observational study

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Abstract

Hypertension is a well-known risk factor for stroke, but the relationship between blood pressure variation (BPV) and prognosis remains unclear. This prospective observational study assessed the association between BPV and early functional outcomes in acute ischemic stroke patients. A total of 871 patients with acute ischemic stroke within 24 h of symptom onset were recruited from the Third Affiliated Hospital of Qiqihar Medical University between 2013 and 2016. Within 6 days of hospitalization, blood pressure was continuously measured from 8:00 to 9:00 every day, and the coefficient of variation (CV) of blood pressure was calculated (including systolic blood pressure [SBP] and diastolic blood pressure [DBP]). The modified Rankin scale was used to evaluate early functional outcomes at discharge. The coefficients of variation of SBP, DBP, and functional outcomes were included as primary outcome variables. Demographic characteristics and medical history were recorded as secondary outcome variables. We found that a greater CV level of SBP and DBP were associated with the poor early functional outcome at hospital discharge, and the odds ratio (OR) and 95% confidence interval (95%CI) of them were 1.56 (1.04–2.35) and 1.99 (1.31–3.03) respectively. A higher standard deviation (SD) of SBP and DBP significantly increased risk of poor early prognosis, OR (95%CI) was 1.78 (1.17–2.71) and 2.25 (1.47–3.45) respectively. Similar results were observed for SBP and DBP. The larger the range of SBP and DBP, the worse is the prognosis. In conclusion, the present study suggests that high BPV is a risk factor for poor early prognosis in acute ischemic stroke.

Abbreviations: AIS = acute ischemic stroke, BPV = blood pressure variability, CI = confidence interval, DBP = diastolic blood pressure, mRs = modified Rankin scale, OR = odds ratio, SD = standard deviation, SBP = systolic blood pressure.

Keywords: blood pressure variability, ischemic stroke, outcome, prognosis

1. Introduction

Although research on stroke has been more in-depth, the mortality rate of stroke worldwide is still as high as 5.5 million per year.[1,2] And it presents a trend toward younger patients.[3] It is well known that hypertension is a well-known risk factor for stroke.[4] However, the potential relationship between post-stroke blood pressure and early prognosis is not fully understood,[5] and the time or optimal value management of arterial hypertension during the acute stroke stage is uncertain.

Gasecki et al showed that the short- and long-term prognosis of stroke was poor after taking antihypertensive drugs.[6] Yet another study suggested that although the effect of blood pressure level on early functional outcome in ischemic stroke patients was not found, increasing blood pressure variation (BPV) was significantly related to impaired function.[7] Actually, BPV commonly appeared to be the result of management of blood pressure in clinic.[8]

Therefore, the aim of this study was to determine the possible relationship between BPV and outcome at hospital discharge among patients with acute ischemic stroke (AIS) in a short-term cohort study and to provide a theoretical basis for antihypertensive therapy in clinical settings.

2. Subjects and Methods

2.1. Patients

This was a prospective, observational study. Patients with AIS were recruited randomly from the Third Affiliated Hospital

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The analysis results generated in this study are included in this article. Further enquiries can be directed to the corresponding author.Supplemental Digital Content is available for this article.

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of Qiqihar Medical University between March 2013 and December 2016 in Qiqihar, China. Patients were confirmed by imaging (cranial CT or brain MRI) according to the diagnostic criteria in China. All participants were recruited within 24 h of symptom onset, and informed consent was obtained from all patients. Exclusion criteria were as follows: patients with transient cerebral ischemia and cerebral hemorrhage; presence of illnesses, including heart and renal disease, malignancy, and autonomic nervous system disease; and patients who could not accurately answer because of memory disorders or psychiatric symptoms.

This study was approved by the Ethics Committee of Qiqihar Medical University ([2016]06) and informed consent was obtained from all patients.

2.2. Data collection

A self-designed questionnaire was used to collect demographic characteristics (age, sex, education level, job, behavioral factors [smoking and drinking], history of coronary heart disease), and physical data (height and weight, fasting blood glucose, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, homocysteine, and imaging data [CT and MRI]) of the patients within the first 24 h after admission to the hospital.

Stroke severity was measured using the modified Rankin scale (mRS) on arrival and on day 7 d, used to assess functional disability and is a formal scale with good liability and validity. The mRS scores range from 0 to 6, with a score of 0 indicating no functional impairment, 5 indicating severe dependency, and 6 denoting death.

Blood pressure was measured at the time of admission and then at 8:00 to 9:00 everyday for the next 5 days in the hospital while the patients were in the supine position using a standard mercury sphygmomanometer according to standard measurements. In the present study, a total of 6 blood pressure values were recorded, and each time, an average value of blood pressure was taken out of 3 measurements.

2.3. Definition of risk factors

The primary outcome of the subjects was evaluated using the mRS, and each group of outcomes was then divided into poor (mRS ≥ 3) and good outcomes (mRS < 3) according to mRS scores. BPV was defined as the coefficient of variation of blood pressure, standard deviation of blood pressure, and range of blood pressure. According to the median BPV, the low-(<median) and high-variability (≥median) groups were classified. BPV and functional outcomes were considered the primary outcome variables.

Demographic characteristics and medical history were recorded as secondary variables. Patients were considered smokers if they smoked at least 1 cigarette per day for a year or more and were still smoking for 6 months before the survey. Those who drank alcohol at least once a month, including social intercourse, or for more than half a year were defined as having a history of drinking alcohol. Dyslipidemia included hypercholesterolemia (total cholesterol ≥ 6.22 mmol/L), hypertriglyceridemia (triacylglycerol ≥ 2.26 mmol/L), low high-density lipoproteinemia (high-density lipoprotein < 1.55 mmol/L), and high-low density lipoproteinemia (low density lipoproteinL ≥ 4.14 mmol/L).[9] The diagnosis of diabetes was defined as a fasting plasma glucose level of 7.1 mmol/L or more,[10] and when homocysteine was ≥15 μmol/L, he was judged to have hyperhomocysteinemia.

2.4. Statistical analysis

Continuous variables expressed as mean ± standard deviation (SD), were compared between groups using Student t-test. Categorical variables were represented as percentages and compared between the groups using the chi-square test. The parameter values of BPV are presented as medians (interquartile ranges). The relationship between BPV and early outcome using odds ratios (ORs) and 95% confidence intervals (95%CIs) was checked with multivariate non-conditional logistic regression. Each BPV parameter was used in a logistic model and adjusted for factors including age, sex, culture, physical activity, income, smoking, drinking, diabetes, coronary heart disease, hospitalization mRS, dyslipidemia, homocysteine, and hyperglycemia. Statistical analyses were performed using SPSS 20.0. All *P* values were 2-tailed, and statistical significance was set at the 5% level.

3. Results

Between March, 2013 and December, 2016, we enrolled 871 patients (577 men, 294 women, the average age was 61.4 ± 10.4 years old) with AIS. A total of 39.95% (n = 248) of AIS patients had a poor early stroke prognosis with an mRS score ≥ 3 at hospital discharge. The baseline characteristics of the patients are summarized in Table 1. Culture, monthly income, baseline mRS, hyperglycemia, and high homocysteine levels were significantly different between patients with good and poor outcomes. There were no significant differences in blood pressure or other variables between the two groups.

Table 2 shows a non-significant relationship between blood pressure levels at admission and an early poor functional outcome after multiple adjustments for potential confounding factors. Compared with those with a systolic blood pressure (SBP) less than 140 mm Hg, multiple-adjusted OR (95%CI) of poor outcome was 0.82 (0.47–1.42), 1.41 (0.79–2.49), and 1.52 (0.71–3.24) among participants, whose SBP were 140 to 159 mm Hg, 160 to 179 mm Hg and 180 to mm Hg, respectively. Compared with those with diastolic blood pressure (DBP) less than 90 mm Hg, multiple-adjusted OR (95%CI) of poor outcome was 1.00 (0.60–1.69), 1.16 (0.66–2.06), and 1.00 (0.50–2.00) among participants with DBP 90 to 99 mm Hg, 100 to 109 mm Hg and 110 to mm Hg, respectively.

Among these patients, 81.4% (n = 709) of them were classified as hypertensive at admission, and the proportion whose blood pressre was extremely high (SBP ≥ 200 mm Hg or DBP ≥ 110 mm Hg) was 12.51%. Figure 1 (the corresponding data are in Appendix 1, Supplemental Digital Content http://links.lww.com/MD/H393) shows the distribution of blood pressure classification six days after admission. The number of patients with elevated blood pressure levels gradually declined, but 24.11% of patients were still classified as extremely hypertensive (SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg) on the sixth day.

Table 3 shows the data characteristics of BPV parameters, including coefficient of variation (CV), SD, and range. BPV was divided into 2 groups according to the median because of their non-normal distribution.

As presented in Table 4, patients with high SBP and DBP variability had a greater risk of poor outcomes than those with low variability, even after multivariate adjustment. Patients with SBP_{CV} ≥ 8 mm Hg were at higher risk of poor outcome: OR (95%CI) was 1.56 (1.04–2.35), compared to SBP_{CV} < 8 mm Hg; the self-care ability those patients with DBP_{CV} ≥ 9 mm Hg was worse, and OR (95%CI) was (1.22–2.78) adjusting for confounding factors. The result was similar to the range and SD: the patients would have a difficult life experience, whose SBP range was higher than 30 mm Hg or (and) DBP range was higher than 20 mm Hg. The OR (95%CI) were 1.55 (1.03–2.34) and 1.95 (1.30–2.94), respectively. When SBP_{SD} and DBP_{SD} were divided into 2 groups with thresholds of 12 mm Hg and 8 mm Hg, respectively, the higher the value, the worse the life status, and the OR (95%CI) were 1.52 (1.00–2.29) and 1.88 (1.25–2.83).

Table 1

Comparisons of baseline characteristics according to functional outcome at 7 days.

	Good outcome (n = 623)	Poor outcome (n = 248)	$\chi 2$	*P*
Age, y			7.285	.06
<50	89(14.29)	32(12.90)		
50–	194(31.14)	65(26.21)		
60–	209(33.55)	78(31.45)		
≥70	131(21.03)	73(29.44)		
Sex (male, n[%])	410(65.81)	167(67.34)	0.185	.67
Culture			7.866	.02
Primary and below	198(31.78)	102(41.13)		
Junior high school	256(41.09)	95(38.31)		
High school and higher	169(27.13)	51(50.56)		
Monthly income, yuan			9.567	.02
<1000	39(6.62)	25(10.12)		
1000–	191(30.65)	76(30.77)		
2000–	178(28.57)	83(33.60)		
>3000	215(34.51)	63(25.51)		
Coronary heart disease	105(16.85)	42(16.94)	0.001	.98
Smoking	275(43.98)	109(43.95)	0.289	.87
Drinking	213(34.08)	87(35.08)	0.062	.80
Baseline mRS ≥ 3	167(26.81)	238(95.97)	341.076	<.001
Hypercholesterolemia	115(18.46)	54(21.77)	1.247	.26
Hypertriglyceridemia	53(8.51)	15(6.05)	1.490	.22
Low high-density lipoproteinemia	62(9.95)	24(9.68)	0.015	.90
High low-density lipoproteinemia	52(8.35)	31(12.50)	0.549	.06
Diabetes	213(34.19)	120(48.39)	15.141	<.001
Hyperhomocysteinemia	213(34.19)	113(45.56)	9.801	<.01

mRs = modified Rankin scale.

Table 2

Multivariable logistic regression analysis of poor outcome associated with blood pressure level.

	Good outcome (n = 623)	Poor outcome (n = 248)	OR (95%CI) Unadjusted	OR (95%CI) Multivariable adjusted
SBP, mm Hg				
<140	156(25.04%)	62(25.00%)	1.0	1.0
140–	238(38.20%)	73(29.44%)	0.77(0.52–1.15)	0.82(0.47–1.42)
160–	152(4.40%)	81(32.66%)	1.34(0.90–2.00)	1.41(0.79–2.49)
>180	77(12.36%)	32(12.90%)	1.05(0.63–1.74)	1.52(0.71–3.24)
DBP, mm Hg				
<90	223(35.79%)	90(36.29%)	1.0	1.0
90–	184(29.54%)	68(27.42%)	0.92(0.63–1.33)	1.00(0.60–1.69)
100	149(23.92%)	59(23.79%)	0.98(0.67–1.45)	1.16(0.66–2.06)
>110	67(10.75%)	31(12.50%)	1.15(0.70–1.87)	1.00(0.50–2.00)

DBP = diastolic blood pressure, CI = confidence interval, OR = odds ratio, SBP = systolic blood pressure.

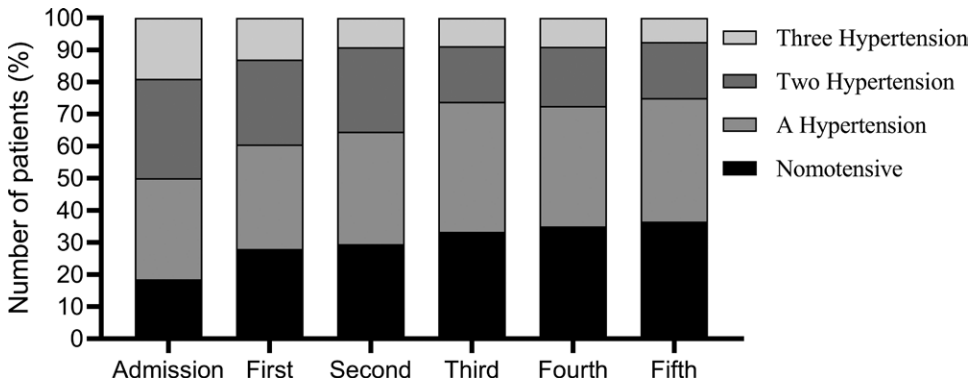

Figure 1. Distribution of blood pressure classification in 6 days from admission.

Table 3

The blood pressure variability parameters characteristics of 871 acute ischemic stroke patients.

Parameters	Mean	Standard deviation	Median	Upper quartile	Lower quartile
SBP_{CV}	8.88	4.73	8.17	5.95	10.91
DBP_{CV}	10.00	9.37	8.80	6.19	12.13
Rang of SBP	34.32	22.12	30	22	42
Rang of DBP	24.21	48.86	20	14	28
SBP_{SD}	13.06	8.45	11.92	8.36	16.07
DBP_{SD}	9.29	17.52	7.76	5.43	10.43

DBP_{CV} = the coefficient of diastolic blood pressure, DBP_{SD} = the standard deviation of diastolic blood pressure, SBP_{CV} = the coefficient of systolic blood pressure, SBP_{SD} = the standard deviation of systolic blood pressure.

Table 4

Multivariable logistic regression analysis of poor outcome associated with blood pressure variability.

	Good outcome	Poor outcome	OR (95%CI)	
	(n = 623)	(n = 248)	Unadjusted	Multivariable adjusted
$SBP_{CV} \geq 8$ mm Hg	48.48%	58.87%	1.52 (1.13–2.05)	1.56 (1.04–2.35)
$DBP_{CV} \geq 9$ mm Hg	43.34%	56.45%	1.70 (1.26–2.28)	1.85 (1.22–2.78)
Rang of SBP > 30 mm Hg	45.91%	53.63%	1.36 (1.01–1.83)	1.55(1.03–2.34)
Rang of DBP > 20 mm Hg	40.61%	56.45%	1.90 (1.41–2.55)	1.95(1.30–2.94)
SBP_{SD} > 12 mm Hg	46.23%	56.05%	1.48 (1.10–2.00)	1.52(1.00–2.29)
DBP_{SD} > 8 mm Hg	42.70%	55.24%	1.66 (1.23–2.23)	1.88(1.25–2.83)

Multivariable model adjusted for age, sex, culture, monthly income, coronary heart disease, smoking, drinking, baseline mRS ≥ 3, hypercholesterolemia, hypertriglyceridemia, low high-density lipoproteinemia, high low-density lipoproteinemia, diabetes, hyperhomocysteinemia.

CI = confidence interval, DBP_{CV} = the coefficient of diastolic blood pressure, DBP_{SD} = the standard deviation of diastolic blood pressure, OR = odds ratio, SBP_{CV} = the coefficient of systolic blood pressure, SBP_{SD} = the standard deviation of systolic blood pressure.

4. Discussion

Several observational studies have indicated that post-stroke hypertension occurs in up to 75% or more of AIS patients.[11] Our present showed that 81.4% of these patients had complications with elevated blood pressure levels on admission to the hospital, and the percentage of patients with SBP > 200 mm Hg or DBP > 110 mm Hg was 12.51%. The number of patients with elevated blood pressure levels gradually declined after hospitalization, but approximately a quarter of the patients still met the accepted criteria for stage two hypertensive (>160/100 mm Hg) on the sixth day. However, our results showed that there was no significant relationship between blood pressure levels at admission and early poor functional outcome after multiple adjustments for potential confounding factors. This result was consistent with the conclusion of Johan-Emil Bager et al[12] and a randomized placebo-controlled study including 2029 patients with blood pressure elevation revealed that there was no remarkably increased risk in the placebo group compared with the blood pressure lowering treatment group.[13]

We further examined the relationship between BPV and the short-term outcomes. According to this study, a higher level of SBPcv or DBPcv was associated with a significantly poor early functional outcome at hospital discharge, and the same trend was seen in the SD and range of SBP and DBP. A study including 1874 patients with ischemic stroke observed that high blood pressure level after AIS is associated with poor clinical outcomes, compared with the lowest quintile of SBP, the OR (95%CI) in the highest quintile were 1.92 (1.15–3.27) and 2.51 (1.69–3.74) respectively for neurological deterioration and a poor functional outcome.[14] Our results were relatively consistent. In addition, previous studies have demonstrated that during the acute phase of stroke, greater BPV is associated with an increased risk of ischemia or hemorrhage, death, and disability.[15,16] One such study by Lancet et al reported that visit-to-visit variability in SBP was a stronger predictor of stroke, but the authors did not find the same for DBP ariability.[17]

The exact mechanism of BPV and short-term prognosis of cerebral infarction remain unknown. Nepal et al pointed out that patients with a large coefficient of variation in blood pressure had a greater pressure on the vascular endothelium of the collateral circulation, which would more easily accelerate bleeding and affect the prognosis.[18] In addition, Kolyviras et al suggested that patients with large variations in blood pressure levels might increase shear force in the vasculature by upregulating endothelial cytokines, thereby inducing vascular inflammation, destroying the blood–brain barrier, promoting the formation of atherosclerotic plaques, and destroying the prognosis.[19] In addition, increased BPV can impair cerebral autoregulation in acute ischemic brain regions. After this function is impaired, blood pressure is increased in a compensatory manner to maintain cerebral blood flow in the ischemic penumbra. Thus, the brain is susceptible to fluctuations in blood pressure, which could lead to instability in cerebral perfusion, such as hypoperfusion or hyperperfusion in the ischemic brain, leading to increased lesion sites, intracranial pressure, and hemorrhage.[20,21]

The main strengths of our study were the BPV defined as CV, SD, and range and the results analysis adjusting for confounders that may influence the conclusion. At the same time, this study had the following limitations. First, blood pressure was measured manually using a mercury sphygmomanometer at 8:00 to 9:00 o'clock every morning for 5 days after hospitalization rather than using a 24 h health monitoring system, which made it impossible to analyze BPV at any time. Second, the outcome of this study analyzed only prognosis at discharge. In addition, some potential relationships need to be investigated; for example, BPV in an acute ischemic stroke setting may differ based on stroke size or location.

5. Conclusions

In summary, our study suggests that BPV may be an important factor in predicting early stroke outcomes; therefore, we

may need to focus more attention on BPV rather than the usual blood pressure level. Meanwhile, a cautious approach to the treatment of hypertension while stabilization of blood pressure should be regarded as a potentially important target in blood pressure management.

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Author contributions

Conceived and designed the experiments: Li jingping, Qiu Changchun and Yang xiujing; Wang ningning,Hu Ying and Jin Ming performed the experiments; Lin Shudong, Zhang Zhilong, Cai Qibo, Deng Yuting were responsible for the diagnosis and collection of patient and control samples; Zhang Hao and Wu Nan analyzed and interpreted the laboratory data. Wang ningning and Jin Ming wrote the manuscript and final approval of the version to be published.
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