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Twenty-four-hour blood pressure variability plays a detrimental role in the neurological outcome of hemorrhagic stroke

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Abstract

Background: Blood pressure variability (BPV) is a modifiable risk factor for stroke. This study was performed to determine the prognostic role of BPV in patients with acute hemorrhagic stroke.

Methods: The data of 131 hospitalized hypertensive patients with spontaneous intracerebral hemorrhage (sICH) were collected. All patients underwent examinations using several neurological scales (Glasgow Coma Scale, National Institutes of Health Stroke Scale, and modified Rankin scale [mRS]) and BP measurements at different time points.

Results: Sex, age, hematoma volume, and neurological scores were not significantly different between patients with a favorable and unfavorable prognosis for sICH. However, significant differences were found in hypertension, diabetes, metabolic syndrome, atrial fibrillation, smoking, and stroke history. The standard deviation (SD), coefficient of variation (CV), and maximum–minimum range (Max–Min) of diastolic BP and the mean, SD, CV, and Max–Min of systolic BP significantly differed between the groups. Statistical analysis also demonstrated correlations between the 90-day mRS score and BPV and between systolic BPV and the 90-day mRS score.

Conclusion: High systolic or diastolic BPV within 24 hours of hemorrhagic stroke onset is associated with the 90-day neurological prognosis. The 24-hour BPV plays a critical role in the neurological outcome of hemorrhagic stroke.

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Blood pressure, variability, stroke, spontaneous intracerebral hemorrhage, computed tomography, neurological outcome

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Introduction

Stroke, also termed cerebrovascular accident, is a clinical emergency and may be caused by cerebrovascular stenosis, blocking, malformation, or rupture. There are two main types of stroke: ischemic stroke and hemorrhagic stroke. Hemorrhagic stroke, which constitutes about 13% of strokes, is caused by a weakened vessel that ruptures, bleeding into and compressing the surrounding brain tissue.[1] The two main types of hemorrhagic stroke are intracerebral and subarachnoid. Increasing numbers of studies are strongly supporting the notion that hypertension is one of the most common causes of both ischemic stroke and hemorrhagic stroke and that it gradually damages blood vessel walls and accelerates the occurrence and development of atherosclerosis.[2–4] Blood pressure variability (BPV), a natural characteristic of blood pressure (BP), is the result of complex interactions between extrinsic environmental and behavioral factors and intrinsic cardiovascular regulatory mechanisms (neural central, neural reflex, and humoral influences). BPV is correlated with the risk of stroke,[5] and BPV is especially detrimental to the occurrence of hemorrhagic stroke. However, the clinical implications of markedly elevated BPV in the setting of acute hemorrhagic stroke are incompletely understood. Whether BPV predicts the clinical outcome of acute stroke remains controversial.[6] Additionally, the significance and management of BP changes in patients with acute hemorrhagic stroke care are unclear. In the present study, we investigated the impact of 24-hour BPV on 90-day outcomes in patients with acute hemorrhagic stroke. The aim of this study was to determine the correlation between the 90-day modified Rankin scale (mRS) score and BPV in patients with acute hemorrhagic stroke and identify the role of BPV in the prognosis of patients with acute hemorrhagic stroke.

Methods

Study population and design

A prospective cohort study was performed from 10 March 2013 to 10 September 2016. All included patients had a diagnosis of hemorrhagic stroke and were from Renmin Hospital, Hubei University of Medicine. The patients were identified by a primary discharge diagnosis code of 431.xx (hemorrhagic stroke) according to the International Classification of Diseases, Ninth Revision. Patients with no primary diagnosis code but with a secondary diagnosis code of 431.xx were also included in this study. The inclusion criteria for hemorrhagic stroke in this study were in line with the 2013 American Heart Association/American Stroke Association guideline. All patients with spontaneous intracerebral hemorrhage (sICH) met the following conditions: age of >18 years, confirmation of hemorrhagic stroke by head computed tomography (CT) scan and/or magnetic resonance imaging (MRI) in combination with clinical history,

presentation <6 hours after sICH onset, and systolic BP of >140 mmHg and/or diastolic BP of >90 mmHg. The exclusion criteria were no CT or MRI examination, inability to confirm sICH, subarachnoid hemorrhage, secondary hemorrhagic stroke due to traumatic head injury, anticoagulant or thrombolytic therapy, other intracranial pathologies, and surgical therapy for intracranial hematoma in patients with hypertensive cerebral hemorrhage. This study was performed in accordance with the relevant guidelines and regulations and approved by the Research Ethics Committee of Hubei University of Medicine. All patients provided written informed consent.

Data collection

A flow chart of this study is shown in Figure 1. All clinical assessments were performed by experienced neurologists. Hospitalized patients with sICH and hypertension were recruited. All patients underwent examinations using various neurological scales and BP measurements at different time points.

Each patient's BP was measured using an electronic sphygmomanometer once every 15 minutes from admission to 1 hour post-admission, once every 30 minutes from 1 to 6 hours post-admission, and once every hour from 6 to 24 hours post-admission.

The sICH-associated hematoma volumes were measured with the simple formula ABC/2, where A is the longest diameter of the hematoma on the CT slice with the largest hematoma area, B is the longest diameter perpendicular to A on the same slice, and C is the approximate number of CT slices with hemorrhage multiplied by the slice thickness.[7–9]

The Glasgow coma scale (GCS), a neurological scale, was used to assess each patient's conscious level. A GCS score of <8 indicated severe impairment of conscious (coma), a GCS score of 8 to 12 indicated moderate impairment, and a GCS score of ≥13 indicated minor impairment. The National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin scale (mRS) were used to evaluate the clinical outcomes at admission, discharge, and 90 days after stroke. The mRS was used to evaluate the neurological deficits both within 6 hours of hospital admission and 90 days after hemorrhagic stroke. An mRS score of 0 to 1 indicated a favorable prognosis for patients with sICH, and an mRS score of 2 to 6 indicated an unfavorable prognosis.

Statistical analysis

IBM SPSS for Windows, version 19.0 (IBM Corp., Armonk, NY, USA) and Excel (Microsoft Corp., Redmond, WA, USA) were used for statistical analysis. The BP and BPV parameters were the mean BP (Mean), maximum BP (Max), minimum BP (Min), range from Max to Min (Max–Min), standard deviation (SD), and coefficient of variation (CV, calculated as $[100 \times SD]/mean$). A univariate analysis was first performed for each parameter to identify the independent variables. The 90-day mRS score was used as a dependent variable. Spearman's rank correlation coefficient test was conducted. Multiple logistics regression was performed to investigate the association between the 90-day mRS score and BPV (systolic BP: Max–Min < 60, $60 \leq$ Max–Min < 80, and Max–Min ≥ 80; diastolic BP: Max–Min < 20, $20 \leq$ Max–Min < 40, and Max–Min ≥ 40). For parameters with normal distributions and homogeneous variances, the significance of differences between the mean values in the two groups was verified using Student's t-test. The chi square test or Fisher's exact test was used for numerical data to analyze the associations between two different variables. A p value of <0.05 indicated statistical significance.

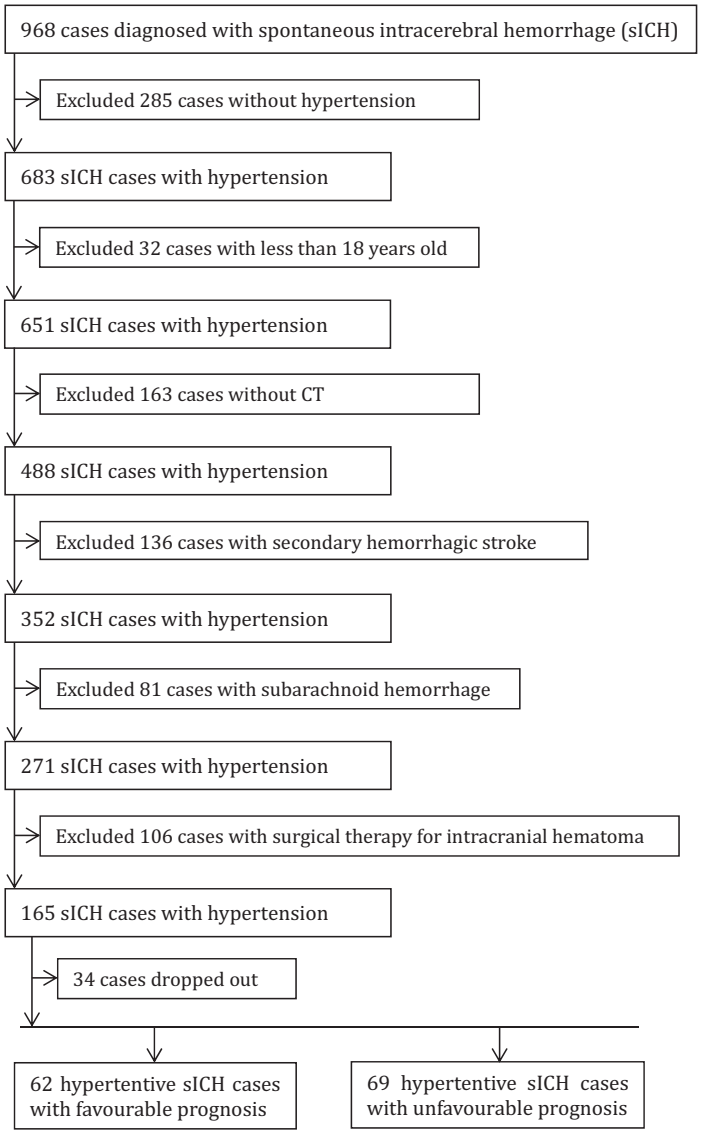

Figure 1. Flow chart of patient recruitment and selection.

Results

Demographic and baseline characteristics

In total, 131 hospitalized patients with sICH and hypertension were recruited. The demographic and baseline characteristics of the patients are shown in Table 1. According to the mRS score, 62 patients had a favorable prognosis and 69 had an unfavorable prognosis. The variables sex, age, hematoma volume, and neurological scales scores (GCS, NIHSS, and mRS scores) were not significantly different

Table 1. Demographic and general characteristics of patients with sICH

Variables	Favorable prognosis (n = 62)	Unfavorable prognosis (n = 69)	*p* value
Sex			0.889
Male	37 (59.7)	42 (60.9)	
Female	25 (40.3)	27 (39.1)	
Age, years	58.22 ± 18.63	62.01 ± 19.32	0.675
Hematoma volume, cm^3	40.23 ± 11.93	43.15 ± 13.28	0.637
Baseline GCS score	12.68 ± 3.62	13.57 ± 4.09	0.369
Baseline NIHSS score	15.32 ± 6.73	16.78 ± 7.13	0.435
Baseline mRS score	2.02 ± 0.16	2.64 ± 0.28	0.512
Hypertension			0.021
Yes	46 (74.2)	61 (88.4)	
No	16 (25.8)	8 (11.6)	
Diabetes			0.018
Yes	24 (38.7)	41 (59.4)	
No	38 (61.3)	28 (40.6)	
Hyperlipidemia			0.334
Yes	28 (45.2)	37 (53.6)	
No	34 (54.8)	32 (46.4)	
Metabolic syndrome			0.008
Yes	23 (37.1)	46 (66.7)	
No	39 (62.9)	23 (33.3)	
Atrial fibrillation			0.105
Yes	21 (33.9)	33 (47.8)	
No	41 (66.1)	36 (52.2)	
Carotid stenosis			0.652
Yes	28 (45.2)	30 (43.5)	
No	34 (54.8)	39 (56.5)	
Alcohol consumption			0.874
Yes	27 (43.5)	31 (44.9)	
No	35 (56.5)	38 (55.1)	
Smoking			0.001
Yes	14 (22.6)	39 (56.5)	
No	48 (77.4)	30 (43.5)	
HHcy, mmol/L	12.16 ± 8.01	13.98 ± 10.31	0.314
Yes (>10 mmol/L)	36 (58.1)	43 (62.3)	
No (≤10 mmol/L)	16 (41.9)	26 (37.7)	
Stroke history			0.002
Yes	15 (24.2)	35 (50.7)	
No	47 (75.8)	34 (49.3)	

Data are presented as n (%) or mean ± standard deviation. HHcy, hyperhomocysteinemia; mRS, modified rankin scale; NIHSS, National Institutes of Health Stroke Scale; sICH, spontaneous intracerebral hemorrhage.

between the favorable and unfavorable prognosis groups according to the univariate analysis of each variable separately. However, significant differences were found in the following risk factors: hypertension, diabetes, metabolic syndrome, atrial fibrillation, smoking, and stroke history ($p < 0.05$).

Table 2. Effects of BPV on 90-day neurological outcome of patients with sICH

Variables	Favorable prognosis(n = 62)	Unfavorable prognosis(n = 69)	*t* value	*p* value
SBP				
Mean	151.23 ± 14.09	164.51 ± 16.32	3.562	0.016
SD	16.85 ± 3.36	19.25 ± 5.91	3.125	0.032
CV	11.82 ± 3.02	13.75 ± 3.87	2.641	0.006
Max–Min	71.08 ± 22.34	82.27 ± 23.64	2.712	0.001
DBP				
Mean	89.10 ± 15.12	92.16 ± 14.78	1.612	0.135
SD	11.32 ± 2.39	13.56 ± 2.97	2.160	0.036
CV	9.63 ± 2.52	12.14 ± 2.18	1.523	0.026
Max–Min	42.36 ± 12.27	52.38 ± 13.29	2.635	0.001

Data are presented as mean ± standard deviation. BPV, blood pressure variability; CV, coefficient of variation; DBP, diastolic blood pressure; Max, maximum; Min, minimum; SBP, systolic blood pressure; SD, standard deviation; sICH, spontaneous intracerebral hemorrhage

Effects of BPV on 90-day neurological outcome of patients with sICH

As shown in Table 2, the independent-samples *t* test revealed significant differences in the following parameters between the favorable and unfavorable prognosis groups: SD, CV, and Max–Min of diastolic BP and Mean, SD, CV, and Max–Min of systolic BP ($p < 0.05$ for all).

Association of greater BPV fluctuation with worse prognosis of sICH

The multiple logistics regression analysis demonstrated a correlation between the 90-day mRS score and BPV (systolic BP: Max–Min < 60, $60 \leq$ Max–Min < 80, and Max–Min $\geq$ 80; diastolic BP: Max–Min < 20, $20 \leq$ Max–Min < 40, and Max–Min $\geq$ 40) ($p < 0.001$) (Table 3). The Spearman correlation analysis revealed a positive correlation between BPV of systolic BP and the 90-day mRS score (Table 4). These results indicate greater fluctuation of BPV and a worse prognosis in patients with sICH.

Discussion

Changes in BP are well known to occur in patients with acute stroke. Both short- and long-term BPV can act as a reliable predictor for stroke prognosis and stroke recurrence. Abundant studies have reported that 24-hour BPV plays a critical role in stroke-induced neurological impairment. The present study has shown that high systolic or diastolic BPV within 24 hours of hemorrhagic stroke onset is associated with the 90-day neurological prognosis.

BPV is considered a distinctive novel risk factor for both cardiovascular and cerebrovascular diseases. BPV is primarily divided into short-term BPV (minutes to hours) and long-term BPV (days to months). Short-term BPV is usually defined as the oscillation of BP within a 24-hour period (minute-to-minute, hour-to-hour, and day-to-night oscillation) in addition to beat-to-beat oscillation (very-short-term BPV). Long-term BPV includes day-to-day, visit-to-visit, and season-to-season variability.[10] Previous studies have clearly shown that enhanced fluctuation of BP induces vascular stiffness and lesion formation, artery

Table 3. Multiple logistic regression analysis of effects of BPV on 90-day neurological outcome of sICH

	SD			CV			Max–Min		
Variables	Max–Min < 60	$60 \leq$ Max–Min < 80	Max–Min ≥ 80	Max–Min < 60	$60 \leq$ Max–Min < 80	Max–Min ≥ 80	Max–Min < 60	60 $\leq$ Max–Min < 80	Max–Min ≥ 80
SBP									
OR (95% CI)	–	2.31 (1.63–3.64)	4.99 (3.86–6.12)	–	4.16 (3.05–5.13)	4.37 (2.57–6.72)	–	1.26 (0.95–2.61)	4.39 (4.01–6.34)
p value	–	0.0012	0.0008	–	0.0056	0.0032	–	0.0001	0.0001
	Max–Min < 20	$20 \leq$ Max–Min < 40	Max–Min ≥ 40	Max–Min < 20	$20 \leq$ Max–Min < 40	Max–Min ≥ 40	Max–Min < 20	$20 \leq$ Max–Min < 40	Max–Min ≥ 40
DBP									
OR (95% CI)	–	1.36 (1.06–1.78)	2.02 (1.86–3.61)	–	1.95 (1.36–3.97)	3.87 (3.02–5.12)	–	1.03 (1.09–2.52)	1.41 (1.35–1.99)
p value	–	0.81	0.009	–	0.23	0.0002	–	0.96	0.0005

The variables adjusted for in the multivariate model were hypertension, diabetes, metabolic syndrome, smoking, and stroke history. BPV, blood pressure variability; CI, confidence interval; CV, coefficient of variation; DBP, diastolic blood pressure; Max, maximum; Min, minimum; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation; sICH, spontaneous intracerebral hemorrhage.

Table 4. Spearman's rank correlation test between BPV and 90-day mRS score

Variables	Coefficient *r*	*p* value
SBP		
SD	0.225	0.009
CV	0.641	0.002
Max–Min	0.312	0.007
DBP		
SD	2.186	0.162
CV	3.501	0.231
Max–Min	4.635	0.138

BPV, blood pressure variability; CV, coefficient of variation; DBP, diastolic blood pressure; Max, maximum; Min, minimum; SBP, systolic blood pressure; SD, standard deviation.

remodeling, and the onset of arteriosclerotic disease.[11] Many clinical trials have demonstrated that short-term and long-term BPV not only independently contribute to cerebrovascular events but also implicate prognostic significance.[12–15] The present study, designed as a clinical investigation of short-term BPV, confirmed that 24-hour BPV after the onset of hemorrhagic stroke is detrimental to the 90-day neurological prognosis. We also found that both systolic and diastolic BPV within 24 hours of hemorrhagic stroke onset determines the 90-day neurological prognosis; this finding differs from preliminary evidence indicating that systolic BPV is independently associated with poor functional outcomes.[16]

During the past decade, increasing numbers of clinical investigations have noted a relationship between BPV and the risk of stroke.[17,18] A significant association has also been established between diastolic BPV and the risk of hemorrhagic but not ischemic stroke. A recent study showed that higher visit-to-visit diastolic BPV contributes to the risk of any stroke and specifically to hemorrhagic stroke, but not ischemic stroke.[19] Several studies have provided evidence that exaggerated BP fluctuations may be harmful and detrimental to stroke recovery.[20,21] The present study showed that short-term (24-hour) diastolic BPV was also associated with the risk of hemorrhagic stroke and determined the neurological outcome 90 days after the onset of hemorrhagic stroke. Overall, both short-term (24-hour) and long-term (visit-to-visit) diastolic BPV has a detrimental role in the risk of hemorrhagic stroke and the neurological outcome. Therefore, amelioration of BPV has been suggested as an additional clinically relevant treatment of cerebrovascular disease.

Increasing evidence implicates that the stroke outcome is strongly influenced by a multitude of variables related either to metabolic homeostasis, the inflammatory response, or cerebral perfusion and hemodynamics.[22–24] All these factors may act either at the site of brain damage or at the systemic level; influence neurovascular recovery, secondary brain damage, and systemic complications; and consequently impact the clinical outcome.[23,25] Accordingly, the ever-growing insight into the stroke pathophysiology and process could aid the identification of the clinical, biochemical, or brain imaging parameters that may improve prognostic algorithms.[26,27] Preclinical and clinical studies have indicated the detrimental role of BPV in the stroke process,[24,27,28] and because many of these variables in the stroke process can be controlled, regulation of BPV could represent a potential therapeutic target.

Most research data mainly focuses on the association between BPV and ischemic stroke, and BPV is associated with poorer functional outcomes of ischemic stroke than other types of stroke.[29,30] However, one prospective study of 608 consecutive patients admitted with acute ischemic stroke demonstrated no association between BPV during the acute phase of ischemic stroke and in-hospital outcomes.[31] Data on the association between BPV in patients with hemorrhagic stroke and functional outcomes are limited. Moreover, the present study had

a small sample and no long-term follow-up. Hence, larger multicenter clinical observation trials with larger sample sizes are needed to clarify the role of BPV in the neurological prognosis of patients with hemorrhagic stroke.

Accruing evidence is showing that a BP-lowering strategy used in the acute setting of sICH may limit the hematoma growth and be potentially beneficial to the stroke outcome.[32–34] Lowering BP in the acute phase of sICH may influence BPV itself, and different classes of anti-hypertensive agents have different effects on BPV.[35–37] Nevertheless, the present study provides no data about the anti-hypertensive drug classes used by the patients, or whether or how BP was lowered in the acute setting. This represents another study limitation. Further experimental research of anti-hypertensive drugs is required to shed new light on the role of BPV in patients with hemorrhagic stroke.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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