

RESEARCH ARTICLE

# Change in blood pressure variability in patients with acute ischemic stroke and its effect on early neurologic outcome

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**Data Availability Statement:** The study data cannot be made publicly available due to restrictions imposed by the Institutional Review Board of Seoul National University Bundang Hospital and HRPP Executive Committee. Interested, qualified researchers may request the data by contacting [rheizer@naver.com](mailto:rheizer@naver.com) or [snuhbirb@gmail.com](mailto:snuhbirb@gmail.com).

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## Abstract

### Background

How short-term blood pressure variability (BPV) is affected in the acute stage of ischemic stroke and whether BPV is associated with early neurologic outcomes remains unclear.

### Methods

Patients who admitted for ischemic stroke within 24 h of symptom onset were consecutively identified between January 2010 and January 2015. BP profiles measured in real-time were summarized into short-term, 24-h time intervals, based on standard deviation (SD) and mean of systolic BP ( $SBP_{SD}$ ) during the first 3 days. The primary outcome was daily assessment of early neurological deterioration (END). The associations between short-term  $SBP_{SD}$  values and the secular trend for primary outcome were examined.

### Results

A total of 2,545 subjects (mean age,  $67.1 \pm 13.5$  years old and median baseline National Institutes of Health Stroke Scale score, 3) arrived at the hospital an average of  $6.1 \pm 6.6$  h after symptom onset.  $SBP_{SD}$  values at day 1 (SD#D1), SD#D2, and SD#D3 were  $14.4 \pm 5.0$ ,  $12.5 \pm 4.5$ , and  $12.2 \pm 4.6$  mmHg, respectively. Multivariable analyses showed that SD#D2 was independently associated with onset of END at day 2 (adjusted odds ratio, 1.08; 95% confidence interval, 1.03–1.13), and SD#D3 was independently associated with END#D3 (1.07, 1.01–1.14), with adjustments for predetermined covariates,  $SBP_{mean}$ , and interactions with daily  $SBP_{SD}$ .

**Competing interests:** The authors have declared that no competing interests exist.

## Conclusion

Short-term BPV changed and stabilized from the first day of ischemic stroke. Daily high BPV may be associated with neurological deterioration independent of BPV on the previous day.

## Introduction

Blood pressure (BP) generally goes through abrupt and rapid changes in the acute stage of ischemic stroke; approximately 80% of stroke patients initially have an elevated BP, which subsequently stabilizes within a few days.[1,2] This abrupt reactive response has been linked to stroke prognosis, that is, the mean value of BP has been established as an important prognostic factor for cardiovascular outcome.

However, BP variability (BPV), another element comprising the underlying theoretical true BP, has yielded inconsistent results.[3] Some studies suggested that high BPV in the acute stage of ischemic stroke exerted an adverse influence on the progress of early neurologic status.[4–7] High BPV during the first 72 h after stroke onset is associated with occurrence of hemorrhagic transformation and growth of ischemic lesion size, which subsequently increase the risk of poor outcome. However, a recent observational study reported the contradictory finding that an increase in BPV in acute stage had no specific association with 3-month outcome in a large stroke population.[8] Post-hoc analysis from the Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) study and Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) supported the this neutral effect of BPV in the acute stage.[9]

Several conditions could account for these conflicting results. First, the time interval for measurement of BPV must be standardized appropriately. Since BP changes rapidly in the acute stage of ischemic stroke, BPV might be variably estimated according to the measurement time interval.[10] In this situation, a short-term period defined as 24 h would appropriately reflect physiological and neurohumoral conditions rather than use of another measurement interval, such as an ultra-short-term (beat-to-beat), or long-term (day-by-day) interval.[11] Second, short-term BPV observation for 3 consecutive days might be advantageous for determination of the time course of BP during the acute reactive response and subsequent stabilization.[12] Third, the acute stage of ischemic stroke is a high-risk period for neurologic worsening, and is a major factor affecting stroke outcome in addition to baseline neurologic severity.[13–15] Therefore, it would be clinically meaningful to investigate daily short-term BPV in the acute stage and to examine its effect on early neurologic deterioration (END).

In this study, daily short-term BPV during the first 3 days of acute ischemic stroke was examined in hospitalized patients who arrived within 24 h of symptom onset. END was prospectively monitored and documented during the same period.[14,16] We aimed to investigate whether short-term BPV and the changing BPV trend affected the onset of END in the acute stage of ischemic stroke.

## Methods

### Standard protocol approval and patient consent

This study was approved by the local Institutional Review Board of Seoul National University Bundang Hospital with a waiver of informed consent because of its retrospective and

observational design, which posed no potential harm to enrolled patients. Prior to analysis, all medical records and personal information were anonymized and de-identified.

## Subjects and data collection

Patients admitted for ischemic stroke at Seoul National University Bundang Hospital, Republic of Korea, who arrived within 24 h of symptom onset were consecutively identified between January 2010 and January 2015. Ischemic stroke is defined as a sudden onset neurologic dysfunction caused by focal cerebral, spinal or retinal infarction confirmed by imaging studies. [17] Demographic and stroke information were collected by reviewing the institution's embedded electronic health records (EHRs) and the hospital's prospective stroke registry. [18]

BP data of enrolled subjects in the acute stage, defined as the time from stroke onset to 72 h after onset, were downloaded from the EHR. Routine hospital management strategy required patients to be admitted to the stroke unit or intensive care unit, to monitor BP according to the physician's decision, based on current stroke guidelines and the patient's condition. [19]

END during hospitalization was prospectively documented, with a final determination made through a weekly consensus meeting, as part of a quality-of-care monitoring and improvement program for hospitalized stroke patients. Neurologic deterioration was operationally defined as worsening by 2 points or more in the total National Institutes of Health Stroke Scale (NIHSS) score. Neurologic deterioration caused by increased intracranial pressure or comorbid medical illness was excluded [16]. END at day 1, day 2, and day 3 (END#D1, END#D2, and END#D3) were separately estimated as a primary outcome. A 3-month poor outcome was defined as a modified Rankin Scale (mRS) score between 3 and 6, and was captured as a secondary outcome. Covariates were predetermined by consideration of previous research and investigator consensus, and included age, diabetes mellitus, baseline NIHSS score, time to arrival, stroke subtype, history of stroke, and recanalization therapy. [14,15,20–26]

## Statistical analysis

Collected BP parameters were summarized into mean SBP ( $SBP_{mean}$ ) at day 1, day 2, and day 3 (M#D1, M#D2, and M#D3) and SD of SBP ( $SBP_{SD}$ ) at day 1, day 2, and day 3 (SD#D1, SD#D2, and SD#D3). Their associations with predetermined baseline characteristics were investigated as appropriate.

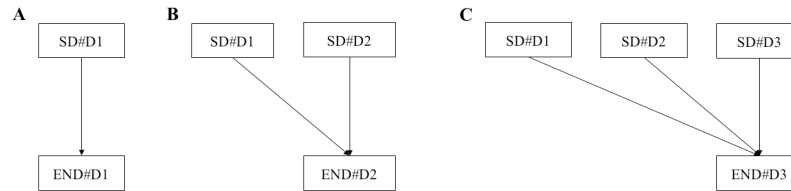
The scheme for analyzing statistical association between  $SBP_{SD}$  and primary outcome is shown (Fig 1). In bivariate analysis, the associations between daily  $SBP_{SD}$  and primary outcomes were compared. The same analyses were performed for  $SBP_{mean}$ . Multivariable logistic regression models were structured using daily short-term BP parameters, with adjustments for pre-selected confounders. These models included interaction effects between the present and previous day for END. We estimated the adjusted odds ratios of daily SD as the secondary outcome.

## Results

### Baseline characteristics

A total of 2,454 patients were enrolled. Their mean age was  $67.1 \pm 13.5$  years old and median baseline NIHSS score was 3 (interquartile range, IQR, 1–9). They arrived at the hospital an average of  $6.1 \pm 6.6$  h after stroke onset, and the median numbers of BP measurements in the acute stage were 26 (IQR, 22–30), 24 (22–26), and 22 (9–25) at day 1, 2, and 3, respectively.

The SD#D1, SD#2, and SD#3 values were  $14.4 \pm 5.0$ ,  $12.5 \pm 4.5$ , and  $12.2 \pm 4.6$  mmHg, and the mean#D1 (M#D1), M#2, and M#3 values were  $134.5 \pm 16.7$ ,  $132.9 \pm 16.7$ , and  $134.7 \pm 16.7$



**Fig 1. Statistical association between  $SBP_{SD}$  and primary outcomes.** Daily  $SBP_{SD}$  values were investigated for END#D1 (A), END#D2 (B), and END#D3 (C). In multivariable analysis, the interaction term  $SD\#D1 \times SD\#D2$  was included in model B and  $SD\#D1 \times SD\#D2$ ,  $SD\#D1 \times SD\#D3$ ,  $SD\#D2 \times SD\#D3$ , and  $SD\#D1 \times SD\#D2 \times SD\#D3$  were included in model C.

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mmHg, respectively. The comparisons of baseline characteristics according to SD#1, SD#2, and SD#3 demonstrated consistent associations with age, sex, baseline NIHSS score, hypertension, and stroke subtype (Table 1).

During hospitalization, 256 (10.4%) subjects experienced END. Of these, 94.5% occurred in the first 3 days; END#D1, END#D2, and END#D3 occurred in 4.1%, 3.5%, and 1.5%, respectively.

## BP parameters and primary outcome

In bivariate analysis, associations between SBP parameters and primary outcome were demonstrated (Fig 2).

The M#D1 was not significantly associated with END#D1. The M#D1 and M#D2 showed significant associations with END#D2; M#D1 and M#D2, but not M#D3, showed significant associations with END#D3 (Fig 2A). SD#D1 values were significantly associated with END#D1; SD#D1 and SD#D2 showed significant associations with END#D2; SD#D1, SD#D2, and SD#D3 showed significant associations with END#D3 (Fig 2B,  $P_s < 0.05$ )

The multivariable logistic regression models showed that SD#D2 increased the odds for END#D2 (adjusted odds ratio, 1.08; 95% confidence interval, 1.03–1.13), independent of the predetermined covariates, previous day BP parameters, and interaction between SD#D1 and SD#D2. SD#D3 independently increased the odds for END#D3 (1.07, 1.01–1.14, Table 2).

## BP parameters and functional outcome

The associations between SBP parameters and 3-month functional outcome were summarized (Table 3). SD#D2 and SD#D3 were independently associated with 3-month poor outcome, with every SD increase of 1 mmHg at day 2 and day 3 increasing the odds for poor outcome by 7% and 4%, respectively.

## Discussion

This study showed that BPV in the acute stage of ischemic stroke generally decreased and stabilized. Under these circumstances in ischemic stroke, daily estimation of BPV would be helpful in determining the risk of END.

The 24-h time window, short-term BPV in patients with ischemic stroke decreased from 14.4 mmHg to 12.2 mmHg during the acute stage. As the mean value of SBP showed a similar range during this period, stabilization of BP was consistent with the decrease in BPV, in other words, fluctuation of BP decreased over time.

A high short-term BPV, meanwhile, showed a significant association with onset of neurologic deterioration, independent of the mean BP and BPV on the previous day. Interestingly,

**Table 1. Association of baseline characteristics with daily SBP<sub>SD</sub>.**

Variables	SD#D1	P	SD#D2	P	SD#D3	P
Age, y, mean ± SD	ρ = 0.14	< 0.001	ρ = 0.26	< 0.001	ρ = 0.20	< 0.001
Sex		< 0.001		< 0.001		0.01
Male (n = 1458)	14.0 ± 5.3		12.2 ± 4.4		12.0 ± 4.6	
Female (n = 983)	15.1 ± 5.3		13.0 ± 4.7		12.5 ± 5.0	
Baseline NIHSS score, median (IQR)	σ = 0.05	0.01	σ = 0.10	< 0.001	σ = 0.09	< 0.001
Recanalization therapy		0.79		0.35		0.02
None (n = 1883)	14.4 ± 5.0		12.5 ± 4.4		12.3 ± 4.8	
IVT-only (n = 192)	14.8 ± 4.8		12.7 ± 4.4		12.4 ± 4.2	
EVT-only (n = 179)	14.4 ± 5.9		12.1 ± 5.0		11.4 ± 4.3	
Combined treatment (n = 187)	14.6 ± 5.0		12.1 ± 4.9		11.7 ± 4.1	
History of stroke		0.15		< 0.001		0.09
Yes (n = 527)	14.8 ± 5.3		13.3 ± 4.8		12.5 ± 4.5	
No	14.5 ± 5.0		12.3 ± 4.4		12.1 ± 4.7	
Hypertension		< 0.001		< 0.001		< 0.001
Yes (n = 1705)	14.8 ± 5.0		13.0 ± 4.5		12.7 ± 4.5	
No	13.6 ± 4.9		11.2 ± 4.3		11.2 ± 4.8	
Diabetes mellitus		0.10		< 0.001		< 0.001
Yes (n = 711)	14.7 ± 5.1		13.2 ± 4.7		12.8 ± 4.8	
No	14.3 ± 5.0		12.2 ± 4.4		12.0 ± 4.5	
Dyslipidemia		0.99		0.35		0.64
Yes (n = 767)	14.5 ± 5.0		12.6 ± 4.5		12.3 ± 4.5	
No	14.5 ± 5.0		12.4 ± 4.5		12.2 ± 4.7	
Atrial fibrillation		0.56		0.03		0.53
Yes (n = 593)	14.5 ± 5.1		12.8 ± 4.8		12.3 ± 4.5	
No	14.4 ± 5.0		12.4 ± 4.4		12.2 ± 4.7	
Stroke subtypes		< 0.001		< 0.001		< 0.001
Small vessel occlusion (n = 399)	15.4 ± 5.4		12.7 ± 4.4		12.8 ± 4.8	
Large artery atherosclerosis (n = 787)	14.5 ± 5.0		13.0 ± 4.4		12.7 ± 4.7	
Cardioembolism (n = 720)	14.3 ± 5.0		12.5 ± 4.6		12.2 ± 4.5	
Other determined (n = 107)	12.3 ± 5.0		10.0 ± 3.3		10.1 ± 3.8	
Undetermined (n = 441)	14.2 ± 4.7		12.5 ± 4.5		11.3 ± 4.4	

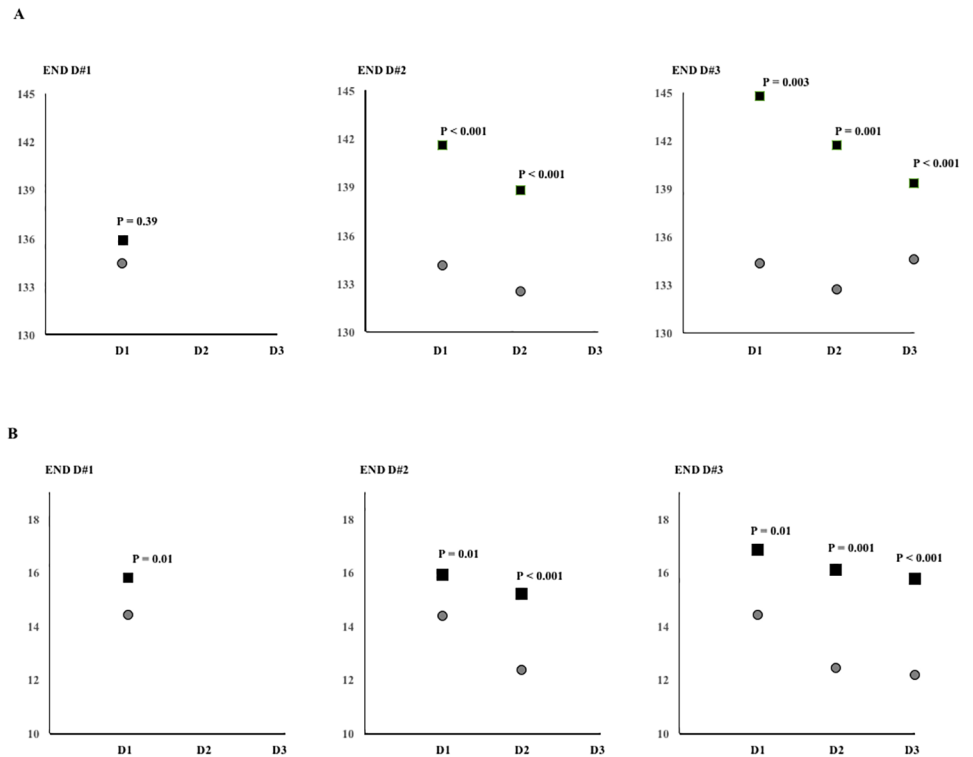
Values are mean ± SD (mmHg) except for interval variables describing correlation coefficient values, with p for parametric and σ for non-parametric variables. P values were obtained by t-test, ANOVA test, Pearson correlation test, and Spearman's correlation test as appropriate. NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation, IQR = interquartile range, IVT = intravenous thrombolysis, and EVT = endovascular treatment.

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daily BPV was not affected by BPV on the previous day. This result shows the need for serial BP monitoring and estimation of BPV. High BPV would assert a harmful effect to maintain the hemodynamic stability in patients impaired the cerebral autoregulation, which, in turn, increase the risk of lesion size growth and new lesions.[27]

BP fluctuates continuously to maintain physiological homeostasis in response to various external and internal conditions, and has been used as an important indicator to track major clinical events, such as cardiac arrest.[28,29] Our findings show how BPV obtained from real-time clinical monitoring can be used in patients with ischemic stroke.

Even though patients with ischemic stroke had similar baseline stroke severity, they presented with various medical and neurologic conditions through acute stage that led to different



**Fig 2. Comparisons of daily SBP parameters according to daily END.** The daily means (A) and standard deviations (B) of SBP are shown as patients with END (box) and without END (circle).

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**Table 2. Associations between daily SBP<sub>SD</sub> and END.**

SBP parameters	Crude analysis			Multivariable analysis		
	END#D1	END#D2	END#D3	END#D1	END#D2	END#D3
SD#D1	1.05 (1.01–1.09)	1.04 (1.01–1.09)	1.08 (1.02–1.13)	1.03 (1.00–1.07)	0.98 (0.94–1.03)	1.01 (0.94–1.07)
SD#D2		1.09 (1.06–1.13)	1.12 (1.07–1.18)		1.08 (1.03–1.13)	1.05 (0.98–1.12)
SD#D3			1.11 (1.06–1.16)			1.07 (1.01–1.14)
					P of SD#1 × SD#2 = 0.13	P of SD#1 × SD#2 = 0.95
						P of SD#1 × SD#3 = 0.06
						P of SD#2 × SD#3 = 0.77
						P of SD#1 × SD#2 × SD#3 = 0.76
Mean#D1	1.01 (0.99–1.02)	1.02 (1.01–1.03)	1.03 (1.02–1.05)	1.01 (1.00–1.03)	1.02 (1.00–1.04)	1.03 (1.00–1.06)
Mean#D2		1.02 (1.00–1.03)	1.03 (1.01–1.05)		1.00 (0.98–1.02)	1.01 (0.97–1.04)
Mean#D3			1.02 (1.00–1.04)			0.99 (0.96–1.02)

Values were crude odds ratios (95% confidence interval) and were estimated using the logistic regression model. Multivariable analyses included BP parameters with adjustments for age, time to arrival, recanalization therapy, hypertension, diabetes, atrial fibrillation, baseline NIHSS score and stroke subtypes.

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**Table 3. Daily SDs of SBP and 3-month functional outcome.**

SBP parameters	OR (95% CI) for poor outcome
SD#D1	1.00 (0.97–1.03)
SD#D2	1.07 (1.04–1.11)
SD#D3	1.04 (1.01–1.07)
Mean#D1	1.01 (1.00–1.02)
Mean#D2	1.01 (0.99–1.02)
Mean#D3	0.99 (0.97–1.03)

Logistic regression models were used to calculate the odds ratios (95% confidence interval), with adjustments for age, time to arrival, recanalization therapy, hypertension, diabetes, atrial fibrillation, baseline NIHSS score, and stroke subtype.

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stroke outcomes. This showed the clinical value of an additional indicator or marker of progress for stroke. BP reflects the change in physiologic conditions and BP monitoring can rapidly detect changes in the patient’s condition. END also showed a time-dependent trend, with most changes occurring in the first few days. Since conventional risk factors for END, such as age, baseline stroke severity, cerebral arterial steno-occlusive lesion,[22] and diabetes mellitus [30] were mostly determined at initial work up process, they cannot be used to assess the change in a patient’s condition.

Previous studies used longer intervals and reported a 14.8–16.5 mmHg SBP<sub>SD</sub> in the acute stage of ischemic stroke.[5,8,27] Since short-term BPV decreased over time, 3-day estimation would yield generally higher values than daily estimation, and the latter method would more promptly show the changing course in stroke victims. Generally, 24-h estimation of BPV is advantageous for demonstrating vascular dysfunction,[31,32] cardiac dysfunction,[33] reduced arterial reflexes, and behavioral and emotional responses.[12] These features of high BPV would demonstrate the detrimental effect on stroke prognosis.

There are several limitations. First, this study was retrospectively conducted using a single hospital database, and had a risk of bias. However, our subjects were consecutively identified from a prospective stroke registry and large amounts of BP data would increase the statistical power. Second, this study only showed an association between BPV and END on a daily basis, and could not explain a causal relationship. Because we aimed to identify the course and impact of short-term BPV, a different study design and more precise analytic tools are needed. Third, BP data were obtained from real-time clinical information and the measurement time interval and numbers were not predetermined. Because median numbers of BP measurements ranged from 22 to 26 times per day and stroke management practice generally measures BP every hour in the acute stage, our estimated values might be similar to those obtained with 24-h ambulatory BP monitoring.

### Author Contributions

**Conceptualization:** Jihoon Kang, Jeong-Ho Hong, Min Uk Jang, Nack Cheon Choi, Beom Joon Kim, Moon-Ku Han, Hee-Joon Bae.

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**Formal analysis:** Jeong-Ho Hong, Nack Cheon Choi, Ji Sung Lee.

**Investigation:** Jeong-Ho Hong, Min Uk Jang, Nack Cheon Choi, Ji Sung Lee.

**Methodology:** Jeong-Ho Hong, Beom Joon Kim.



**Supervision:** Beom Joon Kim, Moon-Ku Han, Hee-Joon Bae.

**Writing – original draft:** Jihoon Kang.

**Writing – review & editing:** Jihoon Kang, Jeong-Ho Hong.

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