Association Between Hyperacute Stage Blood Pressure Variability and Outcome in Patients With Spontaneous Intracerebral Hemorrhage

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Background and Purpose—Increased blood pressure (BP) variability, in addition to high BP, may contribute to adverse outcome in intracerebral hemorrhage. However, degree and association with outcome of BP variability (BPV) in the hyperacute period, 15 minutes to 5 hours after onset, have not been delineated.

Methods—Among consecutive patients with intracerebral hemorrhage enrolled in the FAST-MAG trial (Field Administration of Stroke Therapy-Magnesium), BPs were recorded by paramedics in the field and during the first 24 hours of hospital course. BP was analyzed in the hyperacute period, from 0 to 4–6 hours, and in the acute period, from 0 to 24–26 hours after onset. BPV was analyzed by SD, coefficient of variation, and successive variation.

Results—Among 386 patients with intracerebral hemorrhage, first systolic BP at median 23 minutes (interquartile range, 14–38.5) after onset was median 176 mm Hg, second systolic BP on emergency department arrival at 57 minutes (interquartile range, 45–75) after onset was 178 mm Hg, and systolic BP 24 hours after arrival was 138 mm Hg. Unfavorable outcome at 3 months (modified Rankin Scale, 3–6) occurred in 270 (69.9%). Neither mean nor maximum systolic BP was associated with outcome in multivariable analysis. However, all 3 parameters of BPV, in both the hyperacute and the acute stages, were associated with poor outcome. In the hyperacute phase, BPV was associated with poor outcome with adjusted odds ratios of 3.73 for the highest quintile of SD, 4.78 for the highest quintile of coefficient of variation, and 3.39 for the highest quintile of successive variation.

Conclusions—BPV during the hyperacute first minutes and hours after onset in patients with intracerebral hemorrhage was independently associated with poor functional outcome. Stabilization of BPV during this vulnerable period, in the prehospital and early emergency department course, is a potential therapeutic target for future clinical trials.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00059332.

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In acute spontaneous intracerebral hemorrhage (ICH), elevated blood pressure (BP) has been the focus of intensive pathophysiologic and therapeutic investigation. Higher BPs are associated with early deterioration, hematoma growth, and worse final functional outcome.[1–3] Lowering extremely elevated BP to reduce hemorrhage expansion is recommended in international guidelines.[4,5] However, highly aggressive BP reduction has not shown consistent benefits in randomized trials.[2,6]

In addition to absolute level of BP, BP variability (BPV) may be an important determinant of hemorrhage growth, edema, and final outcome, for example, by challenging cerebral systems to autoregulate cerebral blood flow. Recent

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studies have suggested that BPV may independently contribute to worse outcome after ICH[7–10] but largely focused on BPV in later time window, 6 to 48 hours window after onset, when BPV may be a consequence rather than cause of worsening. Delineation is needed of the relationship between BPV in the first 0 to 4 to 6 hours after onset and ICH outcome. The hyperacute period after stroke onset is the critical stage during which hematoma growth, neurological deterioration, and hemodynamic changes are most prominent. Therefore, we studied the association of BPV and ICH functional outcome in a randomized trial collecting multiple BP measurements in the pre-hospital and early emergency department phase of care.

Methods

We analyzed the data set of the FAST-MAG trial (Field Administration of Stroke Therapy-Magnesium), a phase 3 randomized study of pre-hospital initiation of magnesium for patients with stroke presenting within 2 hours from last known well time.[11–13] The study enrolled 1700 patients with likely acute stroke within 2 hours of onset, and cases with initial systolic BP (SBP) <90 mm Hg or >220 mm Hg were excluded from study entry. Of these, 386 patients with adjudicated final diagnosis of spontaneous ICH were included in this analysis. Treatment of BP was performed as per guideline recommendations and physician' discretion at each institution. The study protocol was approved by the institutional review board at each pre-hospital and hospital study site, and all patients or relevant surrogates gave written informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

For each patient, impairments at study entry were graded by paramedics in the field, including level of consciousness using the Glasgow Coma Scale and neurological deficit severity using the Los Angeles Motor Scale (ranging from 0 to 10, with higher scores indicating more severe motor deficits). In addition, an early post–emergency department (ED) arrival assessment of neurological deficits was performed by study nurses using the National Institutes of Health Stroke Scale. Degree of disability 3 months after stroke on the modified Rankin Scale was assessed by certified study personnel using the Rankin Focused Assessment.[14] For this analysis, favorable 3-month outcome was defined as modified Rankin Scale score of 0 to 2 (functional independence) at 3 months and poor outcome as modified Rankin Scale 3 to 6 (3 is moderate disability requiring some assistance, and 6 is dead).

BP Monitoring and BPV

BP was recorded with an automated electronic device or manual method in the nonparetic arm at 11 timepoints in the first 24 hours. The first BP measure was performed in the field, at time of first paramedic patient assessment, and the second BP assessment was performed on ED arrival. The next 3 BP measures were performed in relation to start of the study agent maintenance infusion in the ED after the completion of the prehospital loading dose. These assessments were obtained before maintenance study medication infusion, 15 minutes and 1 hour after the start of the maintenance infusion. The remaining BP assessments were performed 4, 8, 12,16, 20, and 24 hours after ED arrival. We analyzed BPV in 2 different time frames: hyperacute (from 0 to 4–6 hours after onset) and acute (from 0 to 24–26 hours after onset). We calculated hyperacute BPV from 5 BP measurements: pre-hospital, ED arrival, 15-minute postmaintenance infusion start, 1-hour postmaintenance infusion start, and 4 hours after ED arrival. Acute BPV was calculated from 7 measurements: on arrival in the ED and 4, 8, 12, 16, 20, and 24 hours after ED arrival. Parameters of BPV used were SD of SBP, coefficient of variation (defined as SD/mean×100) of SBP, and successive variation (SV) of SBP. SV of a patient's BP profile is the average squared difference between any 2 successive BP measurements. In contrast with SD and coefficient of variation, the SV reflects the time sequence of measurements and may represent more physiologically relevant variation.[15]

We also measured mean SBP, maximum SBP, and maximum minus minimum SBP. We focused on SBP rather than diastolic BP because prior studies have suggested that diastolic BPV is less physiologically consequential.[16]

Statistical Analysis

Demographic, clinical characteristics, and BPV parameters were compared between patients with favorable and poor outcomes. In addition, the proportion of patients with favorable outcome was compared according to quintiles of each of the BPV parameters. Multivariable logistic analysis was performed to identify the independent BPV parameters associated with outcome. BPV levels were categorized into quintiles rather than using continuous BPV because the BPV variables do not necessarily have a linear relationship with the outcomes. The use of quintiles allowed the existence of linearity or at least monotonicity to be explored. This also allowed for a

Table 1. Comparison of Demographic and Clinical Characteristics Between Patients With Favorable (mRS, 0–2) and Poor (mRS, 3–6) Outcomes

	Favorable Outcome (n=116)	Poor Outcome (n=270)	*P* Value
Age, y (mean±SD)	60.5±12.4	67.6±13.3	<0.0001
Female sex, n (%)	28 (24.1%)	101 (37.4%)	0.01
Clinical characteristics			
Prestroke mRS (mean±SD)	0.0±0.3	0.2±0.7	0.02
Initial LAMS (mean±SD)	3.7±1.1	4.3±1.2	<0.0001
Initial GCS (mean±SD)	14.9±0.6	14.2±1.7	<0.0001
ED NIHSS (mean±SD)	10.5±7.0	22.0±10.9	<0.0001
Magnesium infusion, n (%)	65 (56.0%)	126 (46.7%)	0.09
Vascular risk factor			
Hypertension, n (%)	86 (74.1%)	218 (80.7%)	0.15
Diabetes mellitus, n (%)	16 (13.8%)	55 (20.4%)	0.13
Hyperlipidemia, n (%)	39 (33.6%)	102 (37.8%)	0.44
Atrial fibrillation, n (%)	8 (6.9%)	22 (8.1%)	0.67
Smoking, n (%)	22 (19.0%)	44 (16.3%)	0.52
Coronary artery disease, n (%)	7 (6.0%)	40 (14.8%)	0.02
Any alcohol use, n (%)	61 (52.6%)	112 (41.5%)	0.04
BMI, kg/m^2 (mean±SD)	29.7±6.4	27.6±5.6	0.001
Laboratory variables			
Serum glucose, mg/dL (mean±SD)	134.6±53.4	137.6±44.2	0.57
BUN, mg/dL (mean±SD)	15.5±5.6	18.0±8.4	0.003
Creatinine, mg/dL (mean±SD)	1.0±0.3	1.2±2.3	0.41
eGFR (mean±SD)	82.6±20.9	76.6±23.5	0.02
Leukocyte, ×10^3/μL (mean±SD)	7.8±2.5	8.2±3.2	0.27
Hemoglobin, mg/dL (mean±SD)	14.3±1.5	13.9±1.7	0.02

BMI indicates body mass index; BUN, blood urea nitrogen; ED, emergency department; eGFR, estimated glomerular filtration rate; GCS, Glasgow Coma Scale; LAMS, Los Angeles Motor Scale; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

consistent approach across all analyses. Model 1 was adjusted for baseline stroke severity (Los Angeles Motor Scale dichotomized at 0–3 versus 4–5), age (dichotomized at 70 years), presence of prestroke disability (prestroke modified Rankin Scale >0), and enrolling hospital site. Model 2 was adjusted for variables in model 1 plus other baseline clinical variables known to have an association with the outcome (sex, body mass index, coronary artery disease, alcohol habit, blood urea nitrogen, estimated glomerular filtration rate, and hemoglobin). These variables also had $P<0.10$ in bivariate analyses. Because BPV increases proportionally to increasing BP level, model 3 was adjusted for model 2 variables plus mean SBP. Multivariable analysis was performed separately for each BPV parameters, and therefore, other BPV parameters were not included in the multivariable analysis of each BPV parameter.

Results

Of the 386 patients with ICH in the FAST-MAG study, 116 (31.1%) had a favorable and 270 (69.9%) had a poor outcome at 3 months. Baseline characteristics of patients with favorable and poor outcomes are shown in Table 1. In univariate analysis, with regard to demographic and medical history variables, patients with poor outcomes were older, more frequently female, and had lower body mass index, higher history of coronary artery disease, and less frequent alcohol use. Presenting stroke severity was worse in patients with poor outcome, assessed by Los Angeles Motor Scale and Glasgow Coma Scale, as was early post-ED arrival deficit severity on the National Institutes of Health Stroke Scale. On initial blood testing, patients destined for poor outcome had lower hemoglobin, lower estimated glomerular filtration rate, and higher blood urea nitrogen.

BP data were available in all 386 patients. Of the planned BP measurement, there were no missing BP measurements in the hyperacute period and 3 missing BP measurement in the acute period. The timing and results of the BP assessments up to 48 hours are shown in Table I in the online-only Data Supplement. The first BP assessment, obtained by paramedics in the field, was performed at median 23 minutes (interquartile range [IQR], 14–38.5 minutes) after last known well and showed SBP median 176 mm Hg (IQR, 160–194 mm Hg). The second assessment, on ED arrival, was performed at median 57 minutes (IQR, 45–75 minutes) and showed SBP median 178 mm Hg (IQR, 156–198 mm Hg). By the 24-hour post-ED arrival assessment, SBP median had declined to 138 mm Hg (IQR, 122–154 mm Hg). A mild increase in SBP occurred from 24 to 48 hours, likely in part because of the end of the magnesium infusion, and its mild BP-lowering effects, in the magnesium arm patients.

BPV and Functional Outcome

In univariate analysis, in both the hyperacute and acute time periods, patients with poor outcomes had greater BPV compared with those with favorable outcomes, on all 3 indices of SD, coefficient of variation, and SV (Table 2). Other BP variables associated with poor outcome included mean SBP, maximum SBP, and maximum minus minimum SBP although not minimum SBP. In univariate analysis by quintile groups, the 3 BPV variables were all associated in a graded fashion with poor outcome (P values ranging from <0.01 to <0.001) while maximum and mean SBPs were not associated (P values all >0.10; Figures 1 and 2).

In multivariable logistic regression analysis, parameters of BPV were independently associated with poor outcome in a graded fashion, including after adjustment for mean SBP (Tables 3 and 4). In the hyperacute period, SD, coefficient of variation, and SV values in the highest quintile, compared with the lowest quintile, were associated with higher odds of

Table 2. Blood Pressure Variability Indices Between Favorable and Poor Outcomes

	Total (n=386)	Favorable (n=116)	Poor (n=270)	*P* Value
SBP at baseline	167.0 (28.2)	161.5 (28.5)	172.9 (26.8)	<0.0001
Hyperacute period (0 to 4–6 h after onset)				
Mean SBP	159.5 (22.9)	154.3 (22.8)	165.2 (21.6)	<0.0001
Maximum SBP	181.7 (28.7)	173.8 (27.9)	190.2 (27.1)	<0.0001
Minimum SBP	135.8 (21.5)	134.5 (21.0)	137.3 (22.0)	0.10
SD of SBP	19.3 (10.2)	16.4 (8.7)	22.3 (10.8)	<0.0001
CV of SBP	12.0 (5.9)	10.6 (5.3)	13.5 (6.2)	<0.0001
SV of SBP	22.8 (13.2)	19.1 (10.9)	26.8 (14.4)	<0.0001
Max–Min SBP	45.9 (24.2)	39.3 (21.3)	53.0 (25.2)	<0.0001
Acute period (0 to 24–26 h after onset)				
Mean SBP	145.6 (17.4)	143.1 (18.2)	148.3 (16.2)	0.0001
Maximum SBP	177.9 (29.0)	169.4 (27.0)	187.1 (28.3)	<0.0001
Minimum SBP	118.2 (18.3)	119.1 (16.9)	117.2 (19.6)	0.17
SD of SBP	20.8 (10.3)	17.5 (8.0)	24.4 (11.2)	<0.0001
CV of SBP	14.2 (6.6)	12.1 (5.0)	16.4 (7.3)	<0.0001
SV of SBP	20.7 (9.2)	17.6 (7.2)	24.1 (10.0)	<0.0001
Max–Min SBP	59.7 (29.2)	50.3 (23.0)	70.0 (31.7)	<0.0001

Data are mean mm Hg (SD). CV indicates coefficient of variance; SBP, systolic blood pressure; and SV, successive variation.

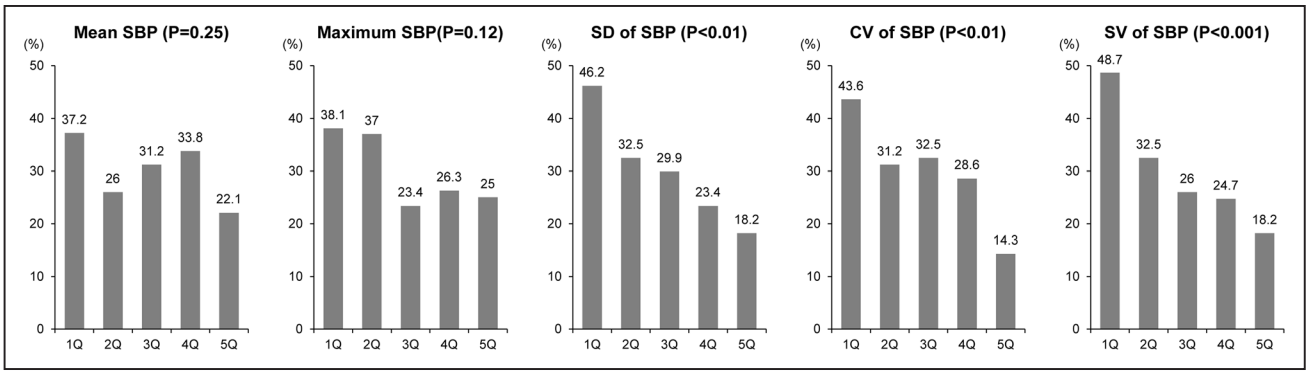

Figure 1. Proportion (as percentage) of patients with favorable outcomes according to quintiles (1Q: lowest quintile group, 5Q: highest quintile group) of each blood pressure variability parameter in the hyperacute period (0 to 4–6 hours after onset). The proportion of patients with favorable outcomes was significantly decreased across the quintiles of SD, coefficient of variation (CV), and successive variation (SV). However, quintiles of maximum systolic blood pressure (SBP) and mean SBP were not correlated with outcome. *P* values are for linear trend.

poor outcome (3–5 fold). In the acute period, the odds of poor outcome increased 5- to 6-fold in the highest quintile of BPV compared with the lowest quintile. In contrast, mean SBP was not consistently associated with poor outcome in either the hyperacute or the acute periods, and maximum BP was not associated with poor outcome in the hyperacute period although was associated in the acute period.

Discussion

This study found that in both the hyperacute first 6 hours and acute first 24 to 26 hours after ICH, BPV was strongly associated with poor functional outcome. The association was independent of clinical predictors, including age and initial deficit severity, and of mean SBP. Furthermore, BPV was more consistently and strongly related to poor outcome than measures of BP magnitude, including mean SBP and maximum SBP. In the hyperacute period, upper quintile BPV values were associated with 3- to 4-fold increased risk of poor outcome compared with lowest quintile BPV values.

These findings confirm and extend prior findings. Our results in the acute period are consistent with several prior studies also showing that BPV in this time window was associated with poor outcome in ICH.[7–9] As far as we are aware, the current study is the first to also investigate the hyperacute period, soonest after ICH onset. Prior studies analyzed BPV during time periods of 5 to 28 hours and 28 to 168 hours after last known well,[7] 1.5 to 25.5 hours after last known well,[8] and from up to 6 to 72 hours after last known well.[9] Our analysis in the hyperacute period, from 15 minutes to 5 hours post-onset, uniquely shows a strong relationship of early BPV with poor outcome.

Because hematoma growth and neurological deterioration are most frequent during the initial several hours after ICH onset,[17,18] BPV in this hyperacute time period may be more likely than later variability to be a cause than a consequence of adverse course. Furthermore, there is less use of antihypertensive therapy in the hyperacute than acute period, so that analysis of BPV in the hyperacute period is potentially less confounded by medication effects and other management decisions.

An interesting finding in the present study was that although mean SBP was associated with outcome in univariate analysis, the association disappeared after adjusting for age, deficit severity, and prestroke disability. In contrast, BPV remained strongly associated with outcome. This finding suggests that fluctuations or changes in BP during the initial hours after stroke onset are more critical for ICH prognosis than the absolute level of BP.

Several mechanisms may connect BPV during the early period and clinical outcomes. Recurrent sudden rises and fluctuation in BP during the active bleeding stage may increase arterial bleeding and hematoma enlargement.[18,19] Conversely, recurrent sudden falls in BP may promote perihematomal

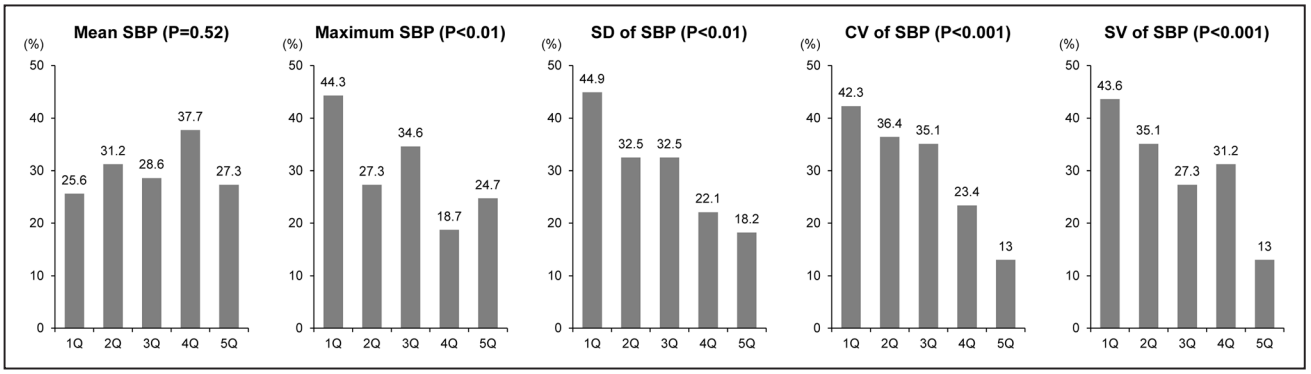

Figure 2. Proportion (as percentage) of patients with favorable outcomes according to quintiles (1Q: lowest quintile group, 5Q: highest quintile group) of each blood pressure variability parameter in the acute period (0 to 24–26 hours after onset). The proportion of patients with favorable outcomes was significantly decreased across the quintiles of SD, coefficient of variation (CV), successive variation (SV), and maximum systolic blood pressure (SBP). However, quintiles of mean SBP were not correlated with outcome. *P* values are for linear trend.

Table 3. OR for Poor Functional Outcome According to the Quintiles of SBP Variability Indices in the Hyperacute (0 to 4–6 Hour) Stage

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Mean SBP						
Q1	Reference	…	Reference	…	…	…
Q2	1.60 (0.76–3.39)	0.22	1.91 (0.87–4.20)	0.11	…	…
Q3	1.27 (0.62–2.62)	0.52	1.34 (0.63–2.85)	0.44	…	…
Q4	1.31 (0.64–2.66)	0.46	1.47 (0.71–3.07)	0.30	…	…
Q5	2.15 (1.02–4.54)	0.05	2.23 (1.01–4.92)	0.05	…	…
Max SBP						
Q1	Reference		Reference		Reference	
Q2	1.34 (0.65–2.77)	0.42	1.34 (0.63–2.84)	0.44	1.42 (0.62–3.28)	0.41
Q3	1.96 (0.93–4.11)	0.08	2.18 (1.00–4.75)	0.05	2.40 (0.90–6.45)	0.08
Q4	2.40 (1.12–5.16)	0.02	2.46 (1.11–5.45)	0.03	2.82 (0.87–9.14)	0.08
Q5	1.84 (0.87–3.86)	0.11	1.76 (0.80–3.91)	0.16	2.14 (0.49–9.42)	0.31
SD SBP						
Q1	Reference		Reference		Reference	
Q2	1.68 (0.82–3.43)	0.15	2.20 (1.02–4.73)	0.04	2.17 (1.01–4.68)	0.0480
Q3	2.30 (1.12–4.72)	0.02	2.51 (1.16–5.41)	0.02	2.43 (1.12–5.28)	0.02
Q4	3.20 (1.51–6.79)	*P*<0.01	3.45 (1.55–7.71)	*P*<0.01	3.34 (1.49–7.50)	*P*<0.01
Q5	3.98 (1.80–8.83)	*P*<0.001	3.98 (1.72–9.22)	*P*<0.01	3.73 (1.58–8.80)	*P*<0.01
CV SBP						
Q1	Reference		Reference		Reference	
Q2	1.64 (0.80–3.35)	0.18	1.95 (0.91–4.16)	0.08	2.05 (0.95–4.39)	0.07
Q3	1.61 (0.79–3.31)	0.19	1.75 (0.83–3.71)	0.14	1.70 (0.80–3.62)	0.17
Q4	2.02 (0.98–4.16)	0.06	2.04 (0.83–3.71)	0.07	2.11 (0.98–4.57)	0.06
Q5	5.16 (2.21–12.0)	*P*<0.001	4.64 (1.95–11.0)	*P*<0.001	4.78 (2.00–11.40)	*P*<0.001
SV SBP						
Q1	Reference		Reference		Reference	
Q2	2.05 (1.01–4.17)	0.05	2.34 (1.11–4.96)	0.03	2.31 (1.09–4.90)	0.03
Q3	2.52 (1.23–5.19)	0.01	2.77 (1.28–5.96)	*P*<0.01	2.72 (1.26–5.87)	0.01
Q4	2.52 (1.20–5.30)	0.01	2.51 (1.16–5.43)	0.02	2.36 (1.08–5.17)	0.03
Q5	3.99 (1.82–8.76)	*P*<0.001	3.64 (1.57–8.47)	*P*<0.01	3.39 (1.44–8.00)	*P*<0.01

Q1 means lowest quintile group and Q5 means highest quintile group of each blood pressure variability indices. Model 1 was adjusted for baseline stroke severity (Los Angeles Motor Scale dichotomized at 0–3 vs 4–5), age (dichotomized at 70 year), presence of prestroke disability, and geographic region of enrolling ambulance. Model 2 was adjusted for variables in model 1 plus sex, body mass index, coronary artery disease, alcohol habit, blood urea nitrogen, estimated glomerular filtration rate, and hemoglobin. Model 3 was adjusted for model 2 variables plus mean SBP. CI indicates confidence interval; CV, coefficient of variation; OR, odds ratio; SBP, systolic blood pressure; and SV, successive variation.

ischemia and ischemia in the territories of remote penetrating arteries.[20] Both BP rise and fall may contribute to disruption of the blood–brain barrier and vasogenic perihematomal edema.[21] Therefore, both higher and lower BP may be detrimental during the hyperacute stage.[22] After the active bleeding period, greater BPV may lead to further cell death in the area of impaired cerebral autoregulation via greater fluctuation in cerebral blood flow.[10] Cerebral perfusion pressure largely depends on systemic BP in the area of ICH and surrounding perihematoma tissue, and fluctuation of BP may directly affect blood flow and brain perfusion, thus amplifying the secondary brain injury in the potentially viable perihematoma area.

A merit of the present study is its inclusion of patients with a wide range of initial SBP levels (90–220 mm Hg). In contrast, the SAMURAI-ICH study (Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement-ICH) enrolled patients with initial SBP >180 mm Hg and INTERACT-2 (Intensive Blood Pressure Reduction in Acute Cerebral

Table 4. OR for Poor Functional Outcome According to the Quintiles of SBP Variability Indices in the Acute (0 to 24–26 Hour) Stage

	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* Value	OR(95%CI)	*P* Value	OR (95% CI)	*P* Value
Mean SBP						
Q1	Reference	…	Reference	…	…	…
Q2	0.56 (0.26–1.19)	0.13	0.72 (0.32–1.58)	0.41	…	…
Q3	1.04 (0.47–2.30)	0.92	1.05 (0.46–2.39)	0.92	…	…
Q4	0.50 (0.24–1.05)	0.0700	0.57 (0.26–1.25)	0.16	…	…
Q5	0.94 (0.44–2.04)	0.8800	1.23 (0.54–2.81)	0.63	…	…
Max SBP						
Q1	Reference		Reference		Reference	
Q2	1.16 (0.57–2.39)	0.68	1.31 (0.62–2.78)	0.48	1.88 (0.84–4.23)	0.13
Q3	1.73 (0.85–3.53)	0.13	1.77 (0.84–3.71)	0.13	3.09 (1.29–7.40)	0.01
Q4	3.76 (1.68–8.42)	<0.01	3.65 (1.58–8.42)	<0.01	8.6 (2.83–26.1)	<0.001
Q5	2.28 (1.07–4.83)	0.03	2.20 (0.98–4.91)	0.06	6.63 (1.95–22.5)	<0.01
SD SBP						
Q1	Reference		Reference		Reference	
Q2	1.59 (0.78–3.24)	0.21	1.78 (0.85–3.75)	0.13	1.85 (0.87–3.93)	0.11
Q3	2.98 (1.41–6.27)	<0.01	3.28 (1.51–7.10)	<0.01	3.39 (1.55–7.41)	<0.01
Q4	2.28 (1.10–4.75)	0.03	2.22 (1.04–4.75)	0.0400	2.38 (1.07–5.26)	0.03
Q5	5.51 (2.35–12.9)	<0.001	4.63 (1.88–11.4)	<0.001	5.06 (1.95–13.1)	<0.001
CV SBP						
Q1	Reference		Reference		Reference	
Q2	1.20 (0.59–2.42)	0.62	1.43 (0.69–2.98)	0.34	1.42 (0.68–2.97)	0.35
Q3	2.79 (1.32–5.87)	<0.01	3.16 (1.45–6.88)	<0.01	3.16 (1.45–6.88)	<0.01
Q4	2.51 (1.19–5.29)	0.02	2.47 (1.14–5.36)	0.02	2.45 (1.13–5.33)	0.02
Q5	6.09 (2.49–14.9)	<0.001	5.02 (1.95–12.9)	<0.001	4.97 (1.93–12.84)	<0.001
SV SBP						
Q1	Reference		Reference		Reference	
Q2	1.49 (0.74–3.02)	0.26	1.51 (0.72–3.17)	0.28	1.53 (0.73–3.21)	0.27
Q3	1.98 (0.97–4.04)	0.06	2.19 (1.03–4.67)	0.04	2.25 (1.05–4.82)	0.04
Q4	2.75 (1.31–5.77)	<0.01	2.44 (1.12–5.30)	0.02	2.53 (1.14–5.59)	0.02
Q5	6.46 (2.60–16.0)	<0.001	5.37 (2.08–13.8)	<0.001	5.60 (2.12–14.7)	<0.001

Q1 means lowest quintile group and Q5 means highest quintile group of each blood pressure variability indices. Model 1 was adjusted for baseline stroke severity (Los Angeles Motor Scale dichotomized at 0–3 vs 4–5), age (dichotomized at 70 year), presence of prestroke disability, and geographic region of enrolling ambulance. Model 2 was adjusted for variables in model 1 plus sex, body mass index, coronary artery disease, alcohol habit, blood urea nitrogen, estimated glomerular filtration rate, and hemoglobin. Model 3 was adjusted for model 2 variables plus mean SBP. CI indicates confidence interval; CV, coefficient of variation; OR, odds ratio; SBP, systolic blood pressure; and SV, successive variation.

Hemorrhage Trial 2) included patients with SBP 150 to 220 mm Hg.[7,8] Therefore, the generalizability of those previous studies might be limited to patients with higher initial SBP.

Our study had several limitations. First, although this study investigated the association between initial BPV and stroke outcome, we did not analyze the effect of BP-lowering medication during the observed period. However, this study focused on the initial 0 to 4–6 hours after stroke onset which might be potentially less confounded by medication effects and other management decisions. Second, although hematoma volume and hematoma expansion have been recognized as critical factors for clinical outcome, association between BPV and hematoma growth could not be identified in this analysis because hematoma volume was not analyzed in the present study. Further studies should investigate the association between early hematoma expansion and early BPV. Third, although entry criteria were broad, the FAST-MAG study excluded patients with mild (no motor deficit) and severe (coma) presentations. Therefore, the study population is not generalizable to the extremes of clinically encountered populations.

Forth, reverse causality cannot be excluded in this observational analysis because larger strokes with a poorer prognosis might give rise to greater BPV rather than BPV per se causing poor outcome.[22] The independent contribution of BPV even after adjustment for stroke severity argues against, but does not exclude, reverse causality.

In conclusion, the results of our study revealed that BPV during the hyperacute first minutes and hours after onset in patients with ICH was independently associated with poor functional outcome at 3 months. Stabilization of BPV during this vulnerable period, in the pre-hospital and early ED course, is a promising therapeutic target for future clinical trials in patients with acute spontaneous ICH.

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Disclosures

None.

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Association Between Hyperacute Stage Blood Pressure Variability and Outcome in Patients With Spontaneous Intracerebral Hemorrhage

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Supplemental Material

Supplemental Table I: Systolic Blood Pressures During First 48 Hours

Time Point	Time Since Last Known Well (minutes), Median (IQR)	Systolic Blood Pressure (mmHg), Median (IQR)
Paramedic assessment (Prehospital)	23 (14-38.5)	176 (160-194)
ED arrival	57 (45-75)	178 (156-198)
Prior to maintenance infusion start		178 (158-203)
15min after maintenance infusion start		177 (157-211)
1hour after maintenance infusion start		163 (147-182)
4hour after ED arrival		147 (131-163)
8hour after ED arrival		140 (125-153)
12hour after ED arrival		138 (123-150)
16hour after ED arrival		138 (122-150)
20hour after ED arrival		138 (124-152)
24hour after ED arrival		138 (122-154)
32hour after ED arrival		140 (126-154)
40hour after ED arrival		142 (129-158)
48hour after ED arrival		146 (130-160)