Original Contribution

Blood Pressure Variability Predicts Poor In-Hospital Outcome in Spontaneous Intracerebral Hemorrhage

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Background and Purpose—There is increasing evidence that higher systolic blood pressure variability (SBPV) may be associated with poor outcome in patients with intracerebral hemorrhage (ICH). We explored the association between SBPV and in-hospital ICH outcome.

Methods—We collected 10-years of consecutive data of spontaneous ICH patients at 2 healthcare systems. Demographics, medical history, laboratory tests, computed tomography scan data, in-hospital treatments, and neurological and functional assessments were recorded. Blood pressure recordings were extracted up to 24 hours postadmission. SBPV was measured using SD, coefficient of variation, successive variation (SV), range and 1 novel index termed functional SV. The effects of SBPV on the functional outcome at discharge were evaluated by multivariate logistic and ordinal regression analyses for dichotomous and trichotomous modified Rankin Scale categorizations, respectively. In secondary analyses, associations between SBPV, history of hypertension, and hematoma expansion were explored.

Results—The analysis included 762 subjects. All 5 SBPV indices were significantly associated with the probability of unfavorable outcome (modified Rankin Scale, 4–6) in logistic models. In ordinal models, SD, coefficient of variation, range, and functional SV were found to have a significant effect on the probabilities of poor (modified Rankin Scale, 3–4) and severe/death (modified Rankin Scale, 5–6) outcomes. Normotensive patients had significantly lower mean SBPV compared with the untreated-hypertension cohort for all SBPV indices and compared with treated-hypertension patients for 3 out of 5 SBPV indices. Lower mean SBPV of treated-hypertension subjects compared with untreated-hypertension subjects was only detected in the SV and functional SV indices (P=0.045). None of the SBPV indices were significantly associated with the probability of hematoma expansion.

Conclusions—Higher SBPV in the first 24 hours of admission was associated with unfavorable in-hospital outcome among ICH patients. Further prospective studies are warranted to understand any cause-effect relationship and whether controlling for SBPV may improve the ICH outcome. **(*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.119.025514.)**

Key Words: blood pressure ■ cerebral hemorrhage ■ computed tomography ■ hematoma ■ hypertension

Acute elevation of blood pressure (BP) level is a common finding after intracerebral hemorrhage (ICH), and it results from the combination of mechanisms, including premorbid hypertension, increased intracranial pressure, activation of neuro-vegetative signaling, and stress. Although elevated BP has been associated with increased risk of early neurological deterioration, the management of BP during the acute phase of ICH remains controversial, and there is still uncertainty about when and how it should be lowered.[1] In randomized trials comparing aggressive versus conservative BP-lowering strategies, early intensive BP reduction was safe and may have attenuated hematoma expansion (HE), but it did not improve the 3-month functional outcome.[2] This suggests that the relationship between BP and ICH outcome may be more complex, and other mechanisms than reducing the absolute BP level may also play a role.

Systolic BP variability (SBPV) is emerging as a potential influence on outcome in patients with ICH. The analyses

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of data from INTERACT2 (The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2),[3] FAST-MAG (Field Administration of Stroke Therapy - Magnesium),[4] and ENRICH (Early Minimally-Invasive Removal of Intracerebral Hemorrhage)[5] trials showed that high SBPV predicted poor functional recovery. This relationship, however, did not emerge in secondary analyses of observational studies that included both ICH and ischemic stroke patients.[6]

The aim of this study, hence, was to further explore the association between 24-hour SBPV and in-hospital ICH outcome in a new cohort of patients with acute spontaneous ICH.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. Before conducting the study, approval was obtained from the Institutional Review Boards at Hennepin County Medical Center and Fairview Health Services in Minneapolis, MN. The data collection protocol has been described previously.[7,8] Briefly, we included 10-year consecutive admission data of spontaneous ICH patients between January 2008 and December 2017 from the 2 healthcare systems in the Twin Cities area. Subjects were identified by using the *International Classification of Diseases* coding system with the primary or secondary diagnosis codes of 431, 432, and 432.9 for the *International Classification of Diseases, Ninth Revision* and I61.0 to I61.9 and I62.9 diagnosis codes for the *International Classification of Diseases, Tenth Revision* (when applicable). We excluded hemorrhage due to other causes.

BP Recording and Variability Measures

BP recordings were extracted on admission, every hour for the first 6 hours postadmission, and every 2 hours from 8 to 24 hours postadmission for a total of 16 BP readings within the first 24 hours. As a routine standard of care, all BP measurements were recorded using an automated cuff at midbiceps level.[9] The mean 24-hour systolic BP (SBP) quantified overall magnitude and SD, coefficient of variation, successive variation (SV), and the difference between maximum and minimum SBP (range) quantified SBPV.[4,10] Additional measures for overall magnitude and SBPV were derived by incorporating the time-dependent nature of SBP measurements using techniques of functional data analysis.[11,12] The functional mean SBP corresponded to the dominant feature in functional principal component analysis. As a measure of SBPV, a functional generalization of SV, called functional SV (FSV), was computed by estimating a scalar summary of the derivative of the latent continuous SBP curve.[13] See the online-only Data Supplement for a description and explicit formula for FSV. We used SBPV as the indicator because it has been reported to be independently associated with death or dependency in ICH, whereas the prognostic significance of diastolic BP variability is uncertain.[14] Nonetheless, we also analyzed diastolic BP variability and mean arterial pressure variability.

Postprocessing of Hematoma From Computed Tomography Scans

Semiautomated planimetry measurement was used to measure hematoma volumes, as previously described.[8,15] We also collected information on hematoma characteristics such as presence (yes/no) of intraventricular hemorrhage, midline shift, hydrocephalus, herniation, multisite hemorrhage, and irregularity of hematoma shape. HE was defined as an increase of ≥ 6 mL or ≥33% of hematoma volume observed between the initial and follow-up computed tomography scans at 24 hours or the closest one.[16] The hematoma shape was categorized as regular or irregular using a binary scoring system, where regular represented a relatively round hematoma with smooth margin and irregular represented a pleomorphic contour of hematoma.[17]

Primary and Secondary Outcomes

The primary outcome was the score on the modified Rankin Scale (mRS) at discharge where it was grouped into dichotomous (mRS: 0–3 versus 4–6) and trichotomous (mRS: 0–2, 3–4, and 5–6) categorical variables. The secondary outcome was the development of HE.

Statistical Analysis

Descriptive analyses were conducted using the median and interquartile range for quantitative variables and the frequency and percentage for qualitative variables. Two preliminary analyses were conducted. First, associations between demographics, clinical, laboratory, and neuroradiologic data with the individual SBPV indices were assessed using Mann-Whitney tests after converting numeric variables to binary by a median split. Second, a screening procedure was applied to all variables to assess their association with the primary outcome using univariate logistic and ordinal regression models (see the online-only Data Supplement for details).

Primary analyses of SBPV were conducted by fitting multivariate logistic (for the dichotomous outcome) and ordinal (for the trichotomous outcome) regression models. Predictors included 1 of the 5 measures of SBPV as the focal variable and controlled for SBP magnitude (mean SBP for SV, coefficient of variation, SV, and range; functional mean SBP for FSV). Other initial control variables identified by the preliminary screening procedure were included to isolate the effects of SBPV. Due to high correlations between the admission neurological scores (National Institutes of Health Stroke Scale, Glasgow Coma Scale, and ICH score), only Glasgow Coma Scale was included as the predictor in the main analysis because it has been reported to be a reliable predictor of ICH mortality.[18] Nonetheless, we also used National Institutes of Health Stroke Scale and ICH score in place of Glasgow Coma Scale to explore sensitivity of results to this choice (see the online-only Data Supplement for details). Finally, we performed backward stepwise model selection using Akaike Information Criterion; focal variables related to SBP were automatically included. Adjusted odds ratios, 95% CI, and *P* values of Wald tests revealed the relationship between SBPV and discharge mRS. Multiple comparisons were controlled using the false discovery rate correction. Because of publication of INTERACT2[3] results in 2013 suggesting beneficial effect of lowering BP, multivariate analyses were also conducted separately for 2 groups defined by admission years 2008 to 2012 and 2013 to 2017 to assess possible differences (see the online-only Data Supplement for details).

Secondary analyses assessed SBPV associations with history of hypertension and HE. For hypertension, subjects were classified as normotensive, treated-hypertension, and untreated-hypertension defined previously.[7] Pairwise 1-sided permutation tests assessed differences in the group mean SBPV values, using the intuition that more severe hypertension status corresponds to larger mean, that is, normotensive <treated- hypertension <untreated-hypertension. Results are reported as unadjusted permutation *P* values and false discovery rate–corrected *P* values. The potential role of SBPV in HE was investigated in the cohort of patients who arrived at the hospital within 3 hours of symptom onset. Univariate logistic regression models with HE as response were fitted for each of the SBPV indices. All statistical analyses were performed using the R software environment (Version 3.5.1; R Core Team, Vienna, Austria).

Results

A total of 1119 subjects were initially identified in our database. Subjects who died within the first 24 hours of admission (n=118), those with >10 missing BP reading records (n=222), and those with "Do Not Resuscitate" care directive (n=17) were excluded. Therefore, 762 subjects were included in the current analysis. Of this cohort, 82.9% (n=632) had between 14 and 16 BP readings, 12.3% (n=94) had between 10 and 13, and only 4.7% (n=36) had between 6 and 10 readings. Characteristics of the excluded patients are reported in Table

Table 1. Mann-Whitney Tests of Equality of Distribution of SBPV Indices for Each Variable Considered in the Regression Models

Variable	FSV	SD	CV	SV	Range
Demographics					
Age (≥ 66 y)	1.644 (0.051)	0.301 (0.437)	0.024 (0.371)	1.422 (0.081)	0.500 (0.404)
Male	0.352 (0.647)	0.064 (0.379)	0.010 (0.914)	0.219 (0.585)	0.500 (0.812)
Clinical features					
Admission GCS (≥14)	2.117 (0.022)	3.141 (0.000)	2.877 (0.000)	5.089 (0.000)	14 (0.000)
Admission NIHSS (≥9)	2.826 (0.001)	3.484 (0.000)	2.685 (0.000)	3.581 (0.000)	15 (0.000)
Admission ICH core (≥2)	1.948 (0.007)	3.447 (0.000)	2.553 (0.000)	4.553 (0.000)	14 (0.000)
History of stroke	1.622 (0.065)	0.788 (0.595)	0.668 (0.303)	0.080 (0.681)	4 (0.429)
History of coagulopathy	4.923 (0.000)	2.157 (0.001)	1.657 (0.003)	1.182 (0.291)	11.5 (0.001)
History of cardiovascular disease	1.236 (0.082)	0.142 (0.779)	0.237 (0.539)	0.945 (0.244)	5 (0.353)
History of cerebrovascular disease	1.220 (0.053)	0.759 (0.326)	0.337 (0.235)	0.241 (0.942)	4 (0.151)
Admission platelet count (≥214×10^9/L)	2.921 (0.013)	2.162 (0.004)	0.768 (0.012)	0.563 (0.099)	8.5 (0.004)
Admission glucose (≥130 mg/dL)	0.759 (0.170)	2.006 (0.000)	1.385 (0.000)	2.975 (0.000)	7 (0.000)
Acute renal failure	5.273 (0.019)	4.999 (0.000)	4.693 (0.001)	6.645 (0.000)	32.5 (0.000)
Comfort care	0.304 (0.777)	2.193 (0.019)	1.480 (0.002)	3.041 (0.000)	6.5 (0.018)
Imaging characteristics					
IVH	1.346 (0.026)	2.632 (0.000)	1.743 (0.000)	3.292 (0.000)	12.5 (0.000)
MLS	0.927 (0.161)	1.904 (0.005)	1.526 (0.000)	3.145 (0.000)	6.5 (0.002)
Hydrocephalus	0.076 (0.493)	1.872 (0.003)	1.561 (0.005)	2.623 (0.006)	7 (0.005)
Herniation	1.119 (0.694)	1.981 (0.013)	1.474 (0.006)	4.374 (0.004)	2.5 (0.116)
Multisite hemorrhage	3.140 (0.184)	0.790 (0.874)	0.820 (0.790)	1.156 (0.631)	2 (0.658)
Irregular hematoma shape	1.047 (0.367)	1.754 (0.026)	1.493 (0.001)	2.466 (0.000)	7 (0.006)
Initial hematoma volume (≥16.4 mL)	0.507 (0.619)	1.257 (0.062)	1.271 (0.007)	1.913 (0.002)	3.5 (0.018)
HE (>33% or > 6 mL)	1.989 (0.024)	0.354 (0.931)	0.548 (0.889)	1.726 (0.109)	0 (0.787)
Infratentorial hemorrhage	3.991 (0.043)	1.869 (0.046)	0.845 (0.146)	0.755 (0.776)	7 (0.047)

Numeric variables were coded as binary using a median split. Reported values are difference in median (*P* value). CV indicates coefficient of variation; FSV, functional SV; GCS, Glasgow Coma Scale; HE, hematoma expansion; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MLS, midline shift; NIHSS, National Institutes of Health Stroke Scale; SBPV, systolic blood pressure variability; and SV, successive variation.

I in the online-only Data Supplement alongside a sensitivity analysis to assess differences between the analyzed cohort and excluded subjects. After correcting for multiple comparisons, excluded subjects were found to have significantly different medians for age, Glasgow Coma Scale, ICH Score, and initial hematoma volume. In addition, the proportions of male subjects, with a history of coagulopathy, history of cerebrovascular disease, comfort care, midline shift, hydrocephalus, herniation, multisite hemorrhage, and irregularity of hematoma shape were different between included and excluded patients.

The associations between SBPV indices and all other variables are reported in Table 1. With the exceptions of sex, history of stroke, history of cardiovascular or cerebrovascular disease, and multisite hemorrhage, all other covariates were significantly related to at least one SBPV index ($P<0.05$). Summary statistics of considered demographic, clinical, radiological, SBP, and hospital length of stay variables are shown in Table 2. Covariates not included in the multivariate analyses of the primary outcome were sex, histories of stroke and cerebrovascular disease, admission platelet count, acute renal failure, and infratentorial hemorrhage. The exploratory analyses showed no association between acute SBPV and length of stay (Figure I in the online-only Data Supplement).

Individual multivariate logistic regression models were trained for each SBPV index (Table 3). Each index was significantly associated with the probability of unfavorable outcome (mRS, 4–6) in the logistic regression models, and SD, coefficient of variation, range, and FSV were found to have a significant effect on the probabilities of poor (mRS, 3–4) and severe/death (mRS, 5–6) outcomes in the ordinal regression models. Findings persisted even after false discovery rate correction of the *P* values. Full model fits for all logistic and ordinal regression are reported in Tables II and III in the online-only Data Supplement. Results corresponding to those of Table 3 for the use of National Institutes of Health Stroke Scale or ICH score and for the pre- and post-2013 cohorts are reported in Tables IV through VI in the online-only Data Supplement. Besides having slightly larger 95% CI due to decreased sample sizes, the results were qualitatively the same for the latter groups as for the full cohort.

Table 2. Summary Statistics of Demographic, Clinical, Radiological, Systolic Blood Pressure, and Length of Hospital Stay Variables

		Dichotomized (Logistic Regression)			Trichotomized (Ordinal Regression)			
Variable	All	mRS (0–3)	mRS (4–6)	*P* Value	mRS(0–2)	mRS (3–4)	mRS (5–6)	*P* Value
Sample size	762	316	446	…	156	372	234	…
Demographics								
Age	66 (23)	63 (22)	68 (23)	0.002	61.5 (20.2)	65.5 (23)	71 (21.8)	<0.001
Male	428 (56.2%)	189 (59.8%)	239 (53.6%)	0.088	98 (62.8%)	203 (54.6%)	127 (54.3%)	0.142
Clinical Features								
Admission GCS	13 (8)	15 (1)	9 (10)	<0.001	15 (1)	14 (4)	6 (7)	<0.001
Admission NIHSS	9 (18)	3 (6)	18.5 (21.8)	<0.001	2 (5)	9 (9)	30 (19.2)	<0.001
Admission ICH score	2 (2)	1 (1)	3 (2)	<0.001	1 (1)	1 (1)	3 (1.8)	<0.001
History of stroke	86 (11.7%)	36 (11.5%)	50 (11.8%)	0.891	10 (6.5%)	49 (13.3%)	27 (12.6%)	0.129
History of coagulopathy	140 (18.4%)	49 (15.5%)	91 (20.4%)	0.086	22 (14.1%)	63 (16.9%)	55 (23.5%)	0.012
History of cardiovascular disease	171 (23.1%)	66 (21.1%)	105 (24.6%)	0.257	33 (21.4%)	76 (20.6%)	62 (28.7%)	0.056
History of cerebrovascular disease	159 (21.5%)	65 (20.7%)	94 (22.2%)	0.631	26 (16.8%)	84 (22.8%)	49 (22.9%)	0.211
Admission platelet count (10^9/L)	213 (89)	212.5 (85)	213 (89)	0.629	211 (83)	213 (81.5)	213 (109)	0.769
Admission glucose, mg/dL	130.5 (60)	118.5 (43.2)	144.5 (73.2)	<0.001	117.5 (39.8)	127 (52.5)	149 (70.5)	<0.001
Acute renal failure	48 (6.3%)	18 (5.7%)	30 (6.7%)	0.565	6 (3.8%)	25 (6.7%)	17 (7.3%)	0.227
Comfort care	200 (26.5%)	0 (0)	200 (45.2%)	0.967	0 (0)	6 (1.6%)	194 (84%)	<0.001
Imaging characteristics								
IVH	333 (43.8%)	81 (25.6%)	252 (56.6%)	<0.001	33 (21.2%)	142 (38.3%)	158 (67.5%)	<0.001
MLS	248 (32.5%)	48 (15.2%)	200 (44.8%)	<0.001	21 (13.5%)	97 (26.1%)	130 (55.6%)	<0.001
Hydrocephalus	121 (15.9%)	19 (6%)	102 (22.9%)	<0.001	9 (5.8%)	41 (11%)	71 (30.3%)	<0.001
Herniation	84 (11%)	9 (2.9%)	75 (16.8%)	<0.001	1 (0.6%)	27 (7.3%)	56 (23.9%)	<0.001
Multisite hemorrhage	40 (5.4%)	7 (2.3%)	33 (7.6%)	0.003	2 (1.3%)	16 (4.4%)	22 (9.6%)	<0.001
Irregular hematoma shape	336 (45.4%)	68 (22.3%)	268 (61.6%)	<0.001	32 (21.3%)	136 (37.6%)	168 (73.7%)	<0.001
Initial hematoma volume (mL)	17.3 (37.4)	6.1 (12.8)	31 (46.7)	<0.001	5 (9.3)	13.3 (25.8)	49.4 (54.6)	<0.001
HE (>33% or > 6 mL)	121 (19.6%)	30 (11.1%)	91 (26.1%)	<0.001	12 (9.2%)	53 (16.1%)	56 (35.4%)	<0.001
Infratentorial hemorrhage	119 (15.6%)	44 (13.9%)	75 (16.8%)	0.279	23 (14.7%)	53 (14.2%)	43 (18.4%)	0.245
BP magnitude								
Mean of SBP	134.9 (16.5)	136.5 (17.7)	134 (15.4)	0.004	137.2 (16.9)	135.3 (18)	133.9 (14.7)	0.002
FmSBP	−1.5 (71)	5 (77.9)	−4.8 (65)	0.009	9.7 (76.5)	0.3 (76.1)	−7 (62.9)	0.003
SBP variability index								
SD	19.6 (10.8)	17.7 (10)	20.7 (10.9)	<0.001	17.2 (8.8)	19.8 (10.4)	21.1 (11.6)	<0.001
CV	14.5 (7.5)	13.1 (7.3)	15.6 (7.5)	<0.001	12.5 (7.1)	14.3 (7.1)	15.8 (8)	<0.001
SV	19.2 (10.6)	17.1 (8)	21 (12)	<0.001	17.1 (8)	18.8 (10.2)	21.7 (11.9)	<0.001
Range	71 (42)	62 (37.5)	75.5 (43)	<0.001	61 (35.2)	72 (38)	76 (44.8)	<0.001
FSV	15 (15.9)	13.9 (15.9)	15.9 (15.3)	0.014	13.7 (13.7)	15.7 (16.2)	15.7 (15.2)	0.076
Hospital stay								
Neuro-ICU stay, d	3 (6)	1 (2)	4 (8)	<0.001	1 (2)	3 (7)	3.5 (7)	<0.001
Total LOS, d	6 (9)	5 (5)	8 (11)	<0.001	5 (4)	8 (10)	5 (10)	0.049

Numeric variables are reported as median (IQR), and binary variables are reported as count (% of total). *P* values correspond to univariate screening tests described in the Supplement. CV indicates coefficient of variation; FmSBP, functional mean SBP; FSV, functional SV; GCS, Glasgow Coma Scale; HE, hematoma expansion; ICH, intracerebral hemorrhage; ICU, intensive care unit; IQR, interquartile range; IVH, intraventricular hemorrhage; LOS, length of stay; MLS, midline shift; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; and SV, successive variation.

Table 3. Summary Statistics for Logistic (mRS: 0–3, 4–6) and Ordinal (mRS: 0–2, 3–4, 5–6) Regression Models

SBPV Index	OR	95% CI	*P* Value	FDR-Corrected *P* Value
mRS: 0–3 and 4–6				
FSV	1.023	(1.004–1.043)	0.018	0.020
SD	1.031	(1.005–1.057)	0.020	0.020
CV	1.044	(1.008–1.082)	0.017	0.020
SV	1.036	(1.011–1.064)	0.007	0.018
Range	1.009	(1.003–1.017)	0.007	0.018
mRS: 0–2, 3–4, and 5–6				
FSV	1.025	(1.007–1.043)	0.007	0.009
SD	1.036	(1.011–1.062)	0.004	0.007
CV	1.052	(1.017–1.089)	0.004	0.007
SV	1.018	(0.995–1.041)	0.129	0.129
Range	1.010	(1.003–1.016)	0.004	0.007

OR are interpreted relative to 1-unit increases for continuous SBPV indices. CV indicates coefficient of variation; FDR, false discovery rate; FSV, functional SV; mRS, modified Rankin Scale; OR, odds ratio; SBPV, systolic blood pressure variability; and SV, successive variation.

Analyses of SBPV and its association with the history of hypertension revealed that normotensive patients had significantly lower mean SBPV compared with untreated-hypertension patients (all SBPV indices) and treated-hypertension patients (SD, range, FSV), see Table 4 and the Figure. Lower mean SBPV of treated-hypertension compared with untreated-hypertension patients was only detected in the SV and FSV indices after false discovery rate correction (P=0.045). None of the SBPV indices were found to be significantly associated with the probability of HE in univariate logistic regression (Table 5).

Corresponding results for all models involving diastolic BP variability and mean arterial pressure variability indices are shown in Tables VII through XIV in the online-only Data Supplement.

Discussion

The key finding of this study was the meaningful association between SBPV and in-hospital outcome in patients with acute ICH, where we did not observe such an association for diastolic BP variability and mean arterial pressure variability (Tables VIII and XI in the online-only Data Supplement). The results were consistent across the categorization of discharge mRS score into dichotomous or trichotomous outcomes and after controlling for a wide set of potential confounders. In comparison to previous studies assessing the same topic,[3–5,10,19] our analyses also adjusted for markers of hematoma severity, including presence of hydrocephalus, irregularity of hematoma shape, and HE, suggesting that the detrimental effects of high SBPV on functional outcome may go beyond their association with already known risk factors for poor prognosis. The lack of any clear-cut association between mean SBP measure and mRS score at discharge could further highlight how protocols advocating purely for the achievement of a specific SBP target level may not be adequate to improve ICH outcome, and other factors, such as the control of SBPV around target SBP and magnitude of SBP reduction, should be considered.

HE is considered an independent risk factor for worsening outcome of ICH.[20] Although we observed a statistically significant association between HE and discharge mRS, none of the SBPV indices indicated a significant association with HE, even after limiting the cohort to the cases with less than 3 hours between symptom onset to initial computed tomography scan. This finding is in line with previous evidence suggesting that a direct effect of SBPV on HE seems unlikely.[3,19,21]

The mechanism by which SBPV affects the outcome in patients with ICH is not fully understood. Impaired BP regulation leading to high SBPV may increase oncotic and hydrostatic pressure gradients in the perihematomal region and further enhance perihematomal edema.[3,22] However, SBPV was higher in older patients and those with severe neurological deficits, which might suggest that the effect of SBPV on ICH prognosis could also be due to other unrecognized factors. It is also worth to note mechanistically that autonomic dysfunction and sympathetic predominance have been associated with proinflammatory cytokine production, hyperglycemia, and increased blood-brain-barrier permeability, all of which may contribute to worse outcomes in ICH patients with increased SBPV without necessarily causing HE.[23–25]

We have also explored the role of baseline hypertension status on SBPV. The distributions of SBPV indices differed based on the hypertension history, where differences were more pronounced between normotensive and hypertensive groups. SV and the novel FSV index were the only ones to detect the hypothesized differences between untreated- and treated-hypertension patients.

One main strength of the present study is the use of a novel SBPV index called FSV. The validity of SD has been questioned as an appropriate index of SBPV, considering that it reflects only the dispersion of values around the mean and does not account for the order in which BP measurements are obtained. Although SV accounts for the order, the relative spacing between BP recordings is not incorporated into this SBPV index, which can differ from patient to patient, particularly in

Table 4. One-Sided Permutation Test *P* Value for SBPV Differences Between Hypertension Groups

Comparison	SD; *P* Value	CV; *P* Value	SV; *P* Value	Range; *P* Value	FSV; *P* Value
Untreated-hypertension > normotensive	0.000 (0.000)	0.006 (0.006)	0.004 (0.005)	0.000 (0.000)	0.000 (0.000)
Treated-hypertension > normotensive	0.002 (0.005)	0.058 (0.073)	0.172 (0.172)	0.004 (0.007)	0.000 (0.000)
Untreated-hypertension > treated-hypertension	0.056 (0.070)	0.086 (0.086)	0.012 (0.045)	0.034 (0.057)	0.018 (0.045)

FDR-corrected *P* Values are given in parentheses. CV indicates coefficient of variation; FDR, false discovery rate; FSV, functional SV; SBPV, systolic blood pressure variability; and SV, successive variation.

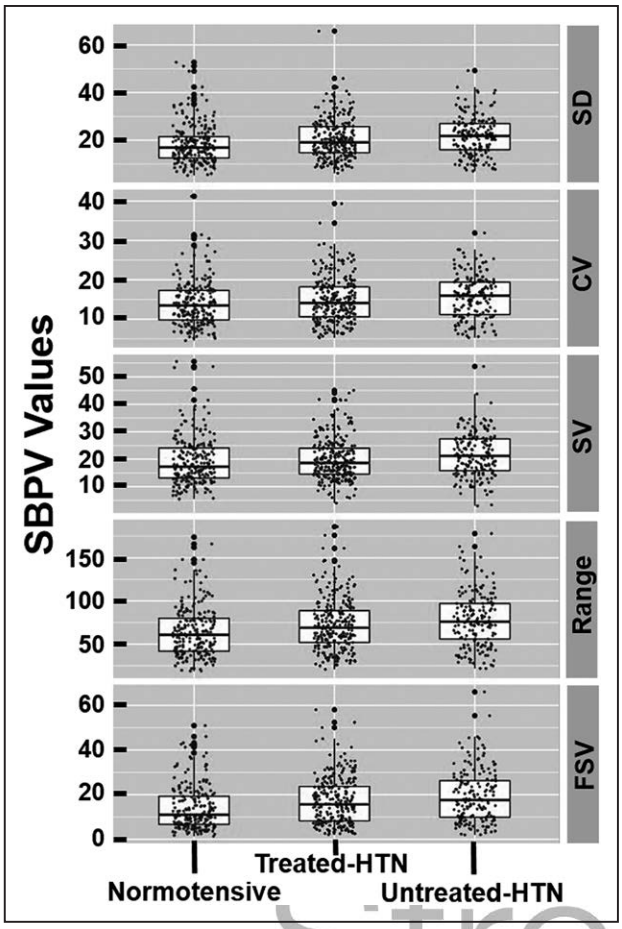

Figure. Box plots of systolic blood pressure variability (SBPV) indices by hypertension (HTN) status. CV indicates coefficient of variation; FSV, functional SV; and SV, successive variation.

retrospective datasets. Unlike other indices, FSV is defined to be independent of the BP measurement intervals and is similar to SV in that it measures variation in successive measurements. It is therefore robust to measurements that are heterogeneous across or between cohorts, due to reasons such as different numbers or spacing of recording times or missing (at random) values. Furthermore, we have assessed SBPV as a continuous covariate, whereas previous studies analyzed SBPV after applying a threshold or discretizing by tertiles, quartiles, or quintiles.[4,5,10] The thresholding approach is designed to account for nonlinear relationships between SBPV indices and log-odds of poor functional outcome, but it is known to result in loss of statistical power and interpretation. Conversely, leaving SBPV indices as continuous predictors allows for a more detailed understanding of how incremental changes in SBPV impact outcome while accounting for other variables. Additional strengths of this study, which allowed for generalizability of its results and provided a scenario similar to routine clinical practice, include the relatively large, multicenter cohort, and the lack of restrictions in the inclusion criteria as concerns the initial BP range and hematoma volume.

Some limitations should be, however, considered in interpreting the findings. The retrospective nature of the study may predispose to methodological issues, such as the reliability of diagnoses, medical histories, and missing data. Furthermore, we could not gauge the true antihypertensive compliance rate, which relied on the reporting of patients, first-degree relatives, and cohabitants. Albeit, compliance with antihypertensive therapy alone may not necessarily equate with well-controlled hypertension. Exclusion of subjects who died during the first 24 hours after admission or with "Do Not Resuscitate" care directives may have also introduced selection bias, despite avoiding the risk of potential bias introduced by the early limitation of care. Finally, only hospital discharge outcomes were considered, although the association of SBPV with long-term functional status has been proposed.[3–5,10,19]

In conclusion, higher SBPV in the first 24 hours of admission was associated with poorer in-hospital outcome after ICH. Although current stroke guidelines focus on a reduction of the absolute BP level, the variability of BP could provide complementary information. Further prospective investigations are warranted to assess the generalizability of our findings, better understand any cause-effect relationship, and explore whether controlling for SBPV may improve the outcome of patients with ICH.

Table 5. Univariate Logistic Regression Analysis of HE and SBPV Indices For Subjects With Less Than 3 Hours From Symptom Onset to Initial CT Scan

SBPV Index	OR	95% CI	*P* Value
FSV	0.984	(0.958–1.009)	0.229
SD	0.976	(0.939–1.013)	0.212
CV	0.961	(0.908–1.014)	0.151
SV	0.989	(0.952–1.024)	0.529
Range	0.997	(0.987–1.006)	0.513

CT indicates computed tomography; CV, coefficient of variation; FSV, functional SV; HE, hematoma expansion; OR, odds ratio; SBPV, systolic blood pressure variability; and SV, successive variation.

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