



Systolic blood pressure variability within 120 hours of admission predicts the functional outcomes at discharge of patients with acute ischemic stroke

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Background: Blood pressure variability (BPV) is a predictor of short- and long-term disability in patients with acute ischemic stroke (AIS). Its effect on more immediate functional outcomes has been seldom studied, and the results are inconsistent. We aimed to determine the role of BPV during the first 5 days of hospitalization in functional status at the time of discharge of patients with AIS.

Methods: We enrolled 134 patients diagnosed with AIS and BPV using standard deviation and coefficient of variation (CV %). These were associated with the dichotomized modified Rankin Scale at discharge using logistic regression.

Results: Patients with unfavorable outcomes were significantly older ($P=0.014$), had a lower body mass index ($P=0.001$), were less likely to present with dyslipidemia ($P=0.001$), had lower serum triglyceride levels ($P=0.012$), had a longer hospitalization period ($P<0.001$), and had a higher mean National Institutes of Health Stroke Scale score at admission ($P<0.001$). After adjusting for multiple confounders, the CV % of systolic blood pressure (SBP) in the first 120 hours after admission had a significant effect on functional disability at discharge.

Conclusion: Variability in SBP in the first 5 days of hospitalization had a deleterious effect on the functional outcomes at discharge of patients with AIS. The role of diastolic BPV seems to be significant only in the first 24 hours of admission; however, further research is required.

Keywords: Ischemic stroke; Treatment outcome; Blood pressure

INTRODUCTION

Acute ischemic stroke (AIS) is the most common type of stroke and a leading cause of disability. In Europe, stroke affects approximately 1.1 million people each year and is responsible for 440,000 annual deaths [1]. Future projections predict that the number of stroke survivors will increase by 27% between 2017 and 2047 due

to lower fatality rates and aging of the population [2]. Therefore, the need to predict the patient's functional outcome after stroke has become a concern for both clinicians and families as it allows optimization of treatment during hospitalization, plan for discharge destination, and assess the need for rehabilitation. Hypertension is the main modifiable risk factor for AIS [3], and its control is crucial for primary and secondary stroke prevention [4-6].

In fact, many systematic reviews and meta-analyses have associated high blood pressure levels in patients with AIS with dependency, deterioration, and death [7,8]. Regardless of the absolute systolic (SBP) and diastolic (DBP) blood pressure levels, blood pressure variability (BPV) is an independent predictor of stroke outcome [9-15]. This association is greater with SBP variability, while the prognostic significance of DBP variability remains uncertain [15]. The detrimental effect of BPV is only partially understood; however, studies show that a rapid decline in blood pressure may extend the ischemic area and the loss of viable penumbra, whereas a sudden increase in blood pressure levels disrupts the blood-brain barrier, causing cerebral edema, elevated intracranial pressure, and augmented risk of hemorrhagic transformation [13].

Most clinical trials have focused on the association of BPV within the first 24–72 hours after AIS with the functional outcome at a 3 to 6 months follow-up, but evidence of a short-term impact is scarce and conflicting. Only a few studies have shown that greater variability in SBP was associated with poor discharge outcomes after AIS [16-18], while other studies do not support this hypothesis [19]. Moreover, most study designs have measured the BPV cumulatively over time, which may alter the statistical effect of specific time intervals after admission. In this study, we aimed to determine the role of BPV during the first 5 days of hospitalization on the functional status at the time of discharge of patients with AIS.

METHODS

Participants and study design

This retrospective cohort study included 134 patients diagnosed with AIS between January 2020 and April 2021. We selected patients who were admitted to our Acute Stroke Unit for up to 48 hours after the onset of symptoms and were previously independent in activities of daily living. The exclusion criteria were as follows: (1) absence of complete tomographic data, blood pressure records, and modified Rankin Scale (mRS) scores; (2) death (mRS 6) or leave during hospitalization; (3) a high degree of functional impairment before the current ischemic event (mRS ≥ 3) and severe depression of consciousness (Glasgow coma scale ≤ 8); (4) presence of systemic disease with potential interference in the patient's functional status or life span: severe psychiatric disease, dementia, hepatic insufficiency, renal insufficiency, pulmonary insufficiency, and hypertensive encephalopathy. The diagnosis of AIS was based on the guidelines for diagnosis and treatment of AIS and was further confirmed using a head computerized tomography.

Data collection and outcome definition

Demographic (age and sex) and anthropometric data (body mass index [BMI]), comorbidities (smoking and drinking history, hypertension, heart failure, diabetes, dyslipidemia, previous stroke, coronary heart disease, and atrial fibrillation), laboratory data (fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein levels), and clinical data (onset-to-door and door-to-needle times) were collected at the time of admission of each patient. An National Institutes of Health Stroke Scale (NIHSS) score was determined by an experienced physician at admission. The mRS was used to assess stroke disability at discharge, and patients were dichotomized as having favorable (mRS 0–2) and unfavorable functional outcomes (mRS 3–5).

Blood pressure monitoring and variability

Blood pressure was measured approximately three times daily (at 08:00–10:00, 13:00–15:00, and 18:00–20:00) by an experienced nurse using an automated electronic sphygmomanometer in the patient's non-paretic arm. Blood pressure was recorded thrice for each evaluation, and the mean value was registered in the electronic medical records as part of routine care. We determined SBP and DBP variability during hospitalization using the standard deviation (SD) and the coefficient of variation (CV %; $100 \times \text{SD} / \text{mean}$) to reduce the influence of the mean blood pressure levels on the dispersion of the data. The SD and CV % were later analyzed using mean and SD. We analyzed BPV at three different and mutually exclusive time intervals (0–24 hours, 25–72 hours, and 73–120 hours) following admission.

Statistical analyses

Descriptive statistics included mean and SD or median and interquartile range (IQR) for continuous variables, and absolute and relative frequency for categorical variables. The distribution of the data was assessed using the Kolmogorov-Smirnov test. Group differences in functional outcomes were studied using the chi-square test, Student t-test, and Mann-Whitney test. Univariate binary logistic regression was performed to study the effect of BPV on functional outcomes at discharge using the CV % at different periods after admission. The odds ratio (OR) for an mRS score of 3 to 5 and their respective 95% confidence interval (95% CI) were calculated. The CV % significantly associated with a poor functional outcome was used for multivariate regression models adjusted for age and BMI in model 1, whereas model 2 was further adjusted for the presence of dyslipidemia, thrombectomy, and NIHSS score at admission. All statistical analyses were performed using the IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA). A

two-tailed P -value < 0.05 was considered statistically significant.

RESULTS

Table 1 describes and compares the characteristics of the 134 enrolled patients between outcome groups. The mean age was 75.2 ± 12.9 years, and 71 patients (53.0%) were males. Patients had a median NIHSS score of 5.0 (IQR, 8) at admission and were discharged after a median hospital stay of 4.0 days (IQR, 6) with a median mRS score of 2.0 (IQR, 2). Based on the latter, we com-

pared 84 patients (62.7%) with favorable functional outcomes against 50 patients (37.3%) with unfavorable outcomes at discharge. Group comparisons showed that patients with unfavorable outcomes were significantly older ($P = 0.014$), had a lower BMI ($P = 0.001$), were less likely to present with dyslipidemia ($P = 0.001$), had lower serum triglyceride levels ($P = 0.012$), had a longer hospitalization period ($P < 0.001$), and had a higher median NIHSS score at admission ($P < 0.001$). The proportion of patients who underwent thrombectomy was lower in those with unfavorable outcomes ($P < 0.001$).

Table 1. Characteristics of the patients with acute ischemic stroke

Variable	Overall (n=134)	Favorable outcome (n=84)	Unfavorable outcome (n=50)	P -value
Age (yr)	75.2±12.9	73.3±13.3	78.4±11.6	0.014
Sex				0.211
Male	71 (53.0)	48 (57.1)	23 (46.0)	
Female	63 (47.0)	36 (42.9)	27 (54.0)	
BMI (kg/m ²)	26.6±4.9	27.8±5.1	24.6±3.9	0.001
Comorbidity				
Smoking	28 (20.9)	21 (25.0)	7 (14.0)	0.130
Drinking	33 (24.6)	22 (26.2)	11 (22.0)	0.586
Hypertension	104 (77.6)	65 (77.4)	39 (78.0)	0.934
Heart failure	38 (28.4)	22 (26.2)	16 (32.0)	0.471
Diabetes	57 (42.5)	35 (41.7)	22 (44.0)	0.792
Dyslipidemia	101 (75.4)	71 (84.5)	30 (60.0)	0.001
Previous stroke	18 (13.4)	10 (11.9)	8 (16.0)	0.501
Coronary heart disease	33 (24.6)	24 (28.6)	9 (18.0)	0.170
Atrial fibrillation	48 (35.8)	31 (36.9)	17 (34.0)	0.734
Laboratory data (mg/dL)				
Fasting blood glucose	136.5±48.7	137.7±55.0	134.4±36.2	0.706
Total cholesterol	170.7±43.3	170.3±45.9	171.5±38.7	0.895
Triglyceride	117.1±53.3	125.0±57.8	102.2±40.3	0.012
HDL cholesterol	47.9±13.0	46.7±13.1	50.2±12.6	0.187
LDL cholesterol	110.0±41.6	109.6±43.6	110.6±38.1	0.904
SBP at admission (mmHg)	149.5±26.5	147.6±24.8	152.6±29.0	0.291
TOAST classification				0.694
Large artery atherosclerosis	73 (54.5)	48 (57.1)	25 (50.0)	
Small vessel occlusion	31 (23.1)	19 (22.6)	12 (24.0)	
Cardioembolism	14 (10.4)	8 (9.5)	6 (12.0)	
Other determined etiology	1 (0.7)	0	1 (2.0)	
Undetermined etiology	15 (11.2)	9 (10.7)	6 (12.0)	
Onset-to-door time (min), median (IQR)	74.0 (285)	60.5 (212)	100.5 (409)	0.069
Door-to-needle time (min), median (IQR)	51.0 (45)	51.0 (49)	50.5 (37)	0.316
IV tPA	28 (20.9)	22 (26.2)	6 (12.0)	0.051
Thrombectomy	15 (11.2)	13 (15.5)	2 (4.0)	0.042
NIHSS score at admission, median (IQR)	5.0 (8)	3.0 (4)	8.5 (9)	<0.001
In-hospital stay duration (day), median (IQR)	4.0 (6)	4.0 (3)	7.0 (11)	<0.001

Values are presented as mean±standard deviation, or number (%) unless otherwise indicated.

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TOAST, trial of Org 10172 in acute stroke treatment; IQR, interquartile range; IV tPA, intravenous tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale.

The mean blood pressure and BPV statistics and their associations with unfavorable functional outcomes at discharge are summarized in Table 2. The average number of blood pressure records per patient was 5.5 ± 2.6 during the first 24 hours after admission, 5.8 ± 2.2 during the 25–72 hours interval, and 4.9 ± 2.1 during the 73–120 hours of hospitalization. There were no significant associations between the mean absolute blood pressure values and clinical outcomes at discharge for all time intervals. Overall, the mean CV % of both SBP and DBP was higher during the 73–120 hours period. The SBP variability showed unadjusted associations with poor functional outcomes at all intervals. However, DBP variability was associated with poor outcomes only during the first 24 hours following admission.

We created a multivariate regression model for each CV % that was significantly associated with the functional outcomes at discharge to adjust for potential confounders found in the group comparison analysis (Table 3). The SBP variability in the first 120 hours after admission increased the risk of poor functional status at discharge after adjusting for age and BMI in model 1 and for remaining confounders in model 2. The effect of DBP variability during the first 24 hours of hospitalization was also associated with a poor functional outcome at discharge, with patients exhib-

iting a three-fold higher risk of unfavorable outcomes at discharge (OR, 3.043; 95% CI, 1.643–5.635; $P < 0.001$) per additional unit of the CV %.

DISCUSSION

Our data demonstrated that increased SBP variability up to 120 hours after admission is associated with a higher risk of disability at discharge when adjusting for demographic and clinical confounders. This is especially useful because it encourages tightening of blood pressure monitoring and its control during the first 5 days of hospitalization as well as weighting clinical decisions based on those readings. However, the mechanism underlying this association remains unclear. While it is true that blood pressure fluctuations contribute to tissue ischemia and lesion expansion, an inverse causality can also be hypothesized given that severe strokes lead to greater autonomic dysfunction and thus higher BPV [13], which was accounted for by correcting our regression model 2 for stroke severity.

However, BMI, serum triglyceride levels, and the prevalence of dyslipidemia were lower in patients with worse outcomes. We hypothesized that the usual body weight loss in the elderly

Table 2. SBP and DBP values and variability and their association with poor functional outcomes at discharge

Time from admission	Overall	Favorable outcome	Unfavorable outcome	Unadjusted OR (95% CI)	P-value
0–24 hr (741 readings)					
Mean SBP	139.7±16.6	138.9±14.4	141.1±19.8	1.008 (0.987–1.030)	0.458
SD SBP	14.0±5.4	12.1±3.6	17.4±6.4	1.242 (1.134–1.360)	<0.001
CV % SBP	10.0±3.6	8.7±2.4	12.3±4.1	1.425 (1.234–1.646)	<0.001
Mean DBP	76.9±10.7	77.2±9.5	76.5±12.4	0.994 (0.961–1.027)	0.714
SD DBP	7.5±3.1	6.0±1.8	10.1±3.2	2.268 (1.684–3.054)	<0.001
CV % DBP	9.8±4.0	7.7±2.3	13.5±3.8	2.198 (1.667–2.898)	<0.001
25–72 hr (757 readings)					
Mean SBP	130.7±16.1	132.0±13.3	128.3±20.1	0.985 (0.962–1.009)	0.211
SD SBP	11.3±5.1	9.1±3.7	14.9±4.9	1.356 (1.216–1.512)	<0.001
CV % SBP	8.7±3.8	7.1±2.8	11.3±3.9	1.502 (1.295–1.743)	<0.001
Mean DBP	72.4±10.6	73.6±10.3	70.1±10.8	0.968 (0.934–1.003)	0.076
SD DBP	8.0±3.8	7.6±4.2	8.5±2.9	1.061 (0.965–1.167)	0.223
CV % DBP	10.9±4.7	10.6±5.1	11.5±3.9	1.042 (0.965–1.124)	0.296
73–120 hr (459 readings)					
Mean SBP	127.3±14.4	128.3±12.7	125.7±16.8	0.987 (0.958–1.017)	0.397
SD SBP	13.4±4.5	11.9±4.0	15.8±4.1	1.273 (1.119–1.447)	<0.001
CV % SBP	10.5±3.4	9.3±3.1	12.6±2.8	1.457 (1.207–1.759)	<0.001
Mean DBP	68.9±10.0	69.8±9.6	67.2±10.6	0.973 (0.932–1.017)	0.230
SD DBP	7.9±3.8	7.5±4.1	8.4±3.0	1.060 (0.947–1.187)	0.308
CV % DBP	11.6±5.8	11.0±6.2	12.8±5.0	1.053 (0.978–1.134)	0.169

Values are mean±standard deviation.

SBP, systolic blood pressure; DBP, diastolic blood pressure; OR, odds ratio; CI, confidence interval; SD, standard deviation; CV %, coefficient of variation.

Table 3. Multivariate logistic regression of independent predictors of an unfavorable functional outcome at discharge using blood pressure variability (CV %) during hospitalization

BPV after admission	Model 1 ^{a)}		Model 2 ^{b)}	
	OR (95% CI)	P-value	OR (95% CI)	P-value
CV % SBP 0–24 hr	1.420 (1.202–1.676)	<0.001	1.386 (1.123–1.712)	0.002
CV % DBP 0–24 hr	2.463 (1.677–3.618)	<0.001	3.043 (1.643–5.635)	<0.001
CV % SBP 25–72 hr	1.595 (1.329–1.914)	<0.001	1.518 (1.219–1.891)	<0.001
CV % SBP 73–120 hr	1.504 (1.207–1.874)	<0.001	1.352 (1.044–1.751)	0.022

CV %, coefficient of variation; BPV, blood pressure variability; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale.

^{a)}Adjusted for age and body mass index; ^{b)}Adjusted for age, body mass index, dyslipidemia, thrombectomy, and NIHSS score at admission.

might justify most of the effect by decreasing the ability of resilience during periods of health deterioration and functional recovery. Regarding serum triglyceride levels and dyslipidemia prevalence, a probable explanation might reside in the tendency to better identify comorbidities in the debilitated patient due to regular follow-up, allowing for better diet and pharmacologic control.

The mean SBP and DBP values were not associated with a higher functional impairment at discharge, although significant effects were indicated in the respective SDs and CVs. We only found unadjusted and adjusted associations of DBP variability in the first 24 hours of hospitalization, but not for the remaining periods. Studies on the short-term influence of DBP variability on the neurological outcomes of patients with AIS are inconsistent. Our results are in line with studies that uncovered that DBP variability contributes to the functional deterioration of patients with AIS [20–23], although the majority of the literature exhibit that SBP variability is a better predictor of worse neurological outcomes [11,14,15,24,25]. While a high DBP variability may impact the ventricular end-diastolic volume and the cerebral perfusion in patients with impaired cerebral blood flow autoregulation, the J-curve relationship between DBP and cardiovascular events may produce a confounding effect on stroke outcomes [26].

Nonetheless, the consistent associations between BPV and worse functional outcomes in patients with AIS found over the years should prompt interventions to optimize both absolute SBP and DBP readings as well as BPV. Current guidelines recommend a permissive hypertension of up to 220/120 mmHg to maintain cerebral perfusion and less than 185/110 mmHg in patients eligible for reperfusion therapy [27]. However, optimal patient management must be tailored individually, as lowering blood pressure levels is done at the expense of increasing BPV. Drug-class effects on interindividual variation in blood pressure may also explain the risk of stroke independent of effects on mean SBP [28], with be-

ta-blockers and angiotensin-converting enzyme inhibitors showing a greater BPV over calcium channel blockers and thiazide diuretics [13].

This study presents several advantages. To our knowledge, this is the first study to evaluate BPV in patients with AIS beyond 24 hours after admission and its relationship with outcomes at discharge. Furthermore, we analyzed BPV as a continuous variable at different time intervals, whereas previous studies considered its cumulative effect by dividing patients into percentiles according to their blood pressure indices [10,11,14,29]. This approach may result in the loss of statistical power, and using a continuous covariate provides a better understanding of the impact of minute and gradual changes in BPV on the functional outcomes.

This study has certain limitations that are worth discussing. Patient data were uncontrolled and retrospectively collected from a single center. Although the extensive exclusion criteria have assured the quality of the data, it may have led to a small sample with a selection bias. In addition, patients were older and had more comorbidities than those in previous studies, which was accounted for in the multivariate regression models. However, we could not adjust for the type of blood pressure medications due to variability in regimens and lack of complete medical records. Therefore, randomized prospective studies are required to corroborate our findings. Nonetheless, we believe our results are useful to improve the care of patients with AIS and guide future investigations.

Variability in SBP in the first 5 days of hospitalization had a deleterious effect on the functional outcomes at discharge of patients with AIS. Our data highlighted a specific time interval for greater blood pressure monitoring and therapeutic management. The contribution of DBP variability to the functional outcomes at discharge seems to be significant only to the first 24 hours of admission; however, further research is required.

ARTICLE INFORMATION

Ethics statement

The study protocol was approved by the Comissão de Ética do HDFF, EPE Ethics Committee, and patient consent was waived because it is a retrospective study.

Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: TP. Data curation: TP, PP, ASC, FA. Formal analysis: TP. Writing—original draft: TP, PP. Writing—review & editing: MLL, TA, AG.

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