Pulse pressure level after acute ischemic stroke is associated with early neurological deterioration

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Abstract. Early neurological deterioration (END) is an unfavorable outcome of acute ischemic stroke and is associated with poor prognosis. Blood pressure variability has been suggested to be involved in the development of END. Therefore, the present study investigated the association between blood pressure variability and the development of END. In the present prospective observational study, 286 patients who developed acute ischemic stroke and then hospitalized within 24 h of stroke onset were recruited. Blood pressure parameters (systolic blood pressure, diastolic blood pressure and pulse pressure) were monitored using a 24 h ambulatory sphygmomanometer within 72 h of ischemic onset. Clinical characteristics were also recorded. Multivariate logistic regression analysis was used to analyze the possible relationship between blood pressure parameters and END after adjustment for confounders. Of the 286 patients in the present study, 64 (22.3%) developed END. Pulse pressure variables, including the mean of 24-h pulse pressure (24-h PP_{MEAN}) and the mean of daytime pulse pressure (Day PP_{MEAN}), were found to be higher in the END group compared with those in the non-END group (P<0.05). Multivariate logistic regression analysis revealed that the blood pressure parameters 24-h PP_{MEAN} [odds ratio (OR), 1.08; 95% CI, 1.01-1.16; P=0.02) and Day PP_{MEAN} (OR, 1.20; 95% CI, 1.011-1.45; P=0.04) were significantly associated with END. These findings suggest that the pulse pressure level fluctuations during the acute stage of ischemic stroke can serve important roles in the development of END, which worsens outcomes after stroke.

Introduction

Ischemic stroke is one of the main causes of disability and mortality in the general population. From 1990 to 2019, there were worldwide increases in the number of cases of ischemic stroke (by 87.55%), and mortalities caused by ischemic stroke increased by 60.68% (1). The estimated age-standardized incidence rate of ischemic stroke in China had a pronounced annual increase of 10% between 1990 to 2019 (1). Neurological deterioration refers to the gradual aggravation of neurological deficit symptoms over a period of time after ischemic stroke onset, which can then be sub-divided into early neurological deterioration (END) and late neurological deterioration (2,3). END after acute ischemic stroke is defined as the worsening of neurological function by physical examination and a neurological scale [the National Institutes of Health Stroke Scale (NIHSS) is the most widely used (4)] during the first 2-3 days after stroke onset (5), where the reported frequency is between 13.0-37.5% (6,7). High degrees of disability and mortality rates are associated with END, supporting its negative impact on patient prognosis (4,8). Therefore, early identification of risk factors for the occurrence of END and active intervention are beneficial for the prognosis of patients. Age (2), initial stroke severity (9), different subtypes of ischemic strokes (10), hyperglycemia (3) and atrial fibrillation (7) have been identified as risk factors of END. The reasons for END include the stroke recurrence, symptomatic hemorrhagic transformation, enlargement of the infarct area and cerebral edema (11). Although previous reports have found that blood pressure (BP) may be associated with END, the specific BP parameters and mechanism involved in END remain unclear (12,13). Therefore, the present study investigated the potential association between BP variability and END by observing the 24-h ambulatory sphygmomanometer parameters in patients with ischemic stroke. It is hoped that results from the present study can offer guidance for establishing a BP management strategy for the acute stage of ischemic stroke and provide a theoretical reference for reducing the incidence of END.

Patients and methods

Patients. In total, 286 patients with acute ischemic stroke that were hospitalized in the China-Japan friendship hospital (Beijing, China) between July 2020 and February 2021 were recruited into the present study. Among them, 199 were men (69.5%). The mean age of the patients was 64±11.36 years. Patients were recruited if they were admitted to hospital within 24 h of stroke onset, a time window allowing for the monitoring of END (2,3). The inclusion criteria for the

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selection of patients in the present study were: i) Aged between 18-80 years; ii) suffering from ischemic stroke; iii) has features of ischemic brain lesions in computer tomography (CT) or magnetic resonance images (MRI) according to the criteria of the World Health Organization; and iv) provided signed informed consent. The exclusion criteria were: i) Patients suffered from cerebral hemorrhage; or ii) a cerebral tumor. Strokes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (14). The evaluation of cerebrovascular status was mainly performed based on magnetic resonance angiography, CT angiography and carotid ultrasound data. The infarct localizations were then collected and classified. The following general and clinical patient characteristics were collected: i) Sex; ii) age; iii) smoking history; iv) history of hypertension, diabetes, hyperlipidemia and atrial fibrillation; v) stroke subtype; and vi) treatment with recombinant tissue plasminogen activators and anti-hypertensive drugs. The anti-hypertensive drugs classified include angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blockers and calcium channel blockers. Multiple drugs use indicates two or more drugs use in the anti-hypertension therapy.

BP parameter measurements. The 24-h ambulatory BP of all patients was monitored using a 24-h ambulatory sphygmomanometer (Mobil-O-Graph; IEM GmbH) within 7 days of stroke onset. Blood pressure was measured non-invasively as previously described (10,11) The interval time for blood pressure measurement was set to be once every 30 min during the day (6:00 a.m. to 10:00 p.m.), and once every 60 min during the night (10:00 p.m. to 6:00 a.m. the next day). Each participant had at least 34 BP measurements collected in a 24 h period. The BP variability was described using parameters (such as the mean, standard deviation and coefficient of variation) for each of systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP). The mean, standard deviation and coefficient of variation [BP SD x100]/BP mean) were calculated and considered to be the parameters of BP variability. In total, two trained physicians (PL and LWZ) assigned the NIHSS score (15). Every patient was evaluated twice a day after admission. END was defined as an increase of ≥2 points in the NIHSS score, an increase of ≥1 points in the 'Level of Consciousness' or 'Motor' items of the NIHSS subscale, or the development of any new neurological deficit (central ataxia) during the first 72 h of stroke onset (2,3). The present study was approved by the Ethics review board of China-Japan friendship hospital (approval no. 2020-90-K55) and was conducted in accordance with the institutional guidelines. Written informed consent was provided by all patients.

Statistical analysis. Categorical variables were summarized as N (%), whereas continuous variables were expressed as the mean ± standard deviation or as median and interquartile range. Clinical characteristics and BP parameters of patients with and without END were compared. Pearson $\chi 2$ test or Fisher's exact test was used for categorical variables. Unpaired student's t-test or the Mann-Whitney U test was used for the continuous variables. Univariate logistic regression analysis was used to analyze the relationship between the clinical characteristics, BP parameters and END. The choice of potential confounders (age, history of stroke, atrial fibrillation and stroke classification) for multivariable models was primarily based on a review of previous studies (7,16-18). Multivariate logistic regression analyses were applied to investigate any independent associations between the BP parameters and END.

Results

Patient characteristics. A total of 286 patients who met the research criteria were recruited into the present study. In total, 64 cases (22.3%) had END (END group) and 222 cases (77.7%) did not have END (non-END group). The general clinical characteristics of the two groups are shown in Table I. No significant differences in age, sex, previous history of underlying conditions, infarct localizations and smoking were observed between the two groups. The proportion of small-vessel occlusion stroke patients (51.56%) was markedly higher compared with that of large artery atherosclerotic stroke patients (38.73%) in the END group, although the difference was not statistically significant. No significant difference in treatment, including the use of recombinant tissue plasminogen activator thrombolytic therapy and anti-hypertensive drugs, could be observed between the two groups.

BP parameters. In terms of BP parameters, the 24-h PP_{MEAN} (P=0.03), Day SBP_{MEAN} (P=0.04) and Day PP_{MEAN} (P=0.01) in the END group were higher than those in the non-END group, where the difference was statistically significant (Table II).

According to the univariate logistic analysis (Table III), the BP variables: 24-h PP_{MEAN} [odds ratio (OR), 1.02, 95% CI, 1.00-1.04], Day SBP_{MEAN} (OR, 1.02, 95% CI, 1.00-1.03), Day PP_{MEAN} (OR, 1.03, 95% CI 1.01-1.05) and Night SBP_{SD} (OR, 1.06, 95% CI, 1.00-1.13) showed an association with the occurrence of END. The results of the association between the other tested clinical characteristics and the occurrence of END from the univariate logistic analysis are shown in Table SI. Multivariate logistic regression analysis found that stroke history (OR, 0.29; 95% CI, 0.10-0.74; P=0.02), 24-h PP_{MEAN} (OR, 1.08, 95% CI, 1.01-1.16; P=0.02), and Day PP_{MEAN} (OR, 1.20, 95% CI, 1.011-1.45; P=0.04) were independently associated with the occurrence of END (Table IV).

Discussion

END in patients with ischemic stroke is a difficult obstacle in stroke management. Early identification and prevention of the risk factors for END can improve the prognosis of ischemic stroke (19). A previous study of 80 patients with middle cerebral artery infarction found that increases in BP variability was associated with the expansion of infarct signals on MRI diffusion-weighted imaging (20). Based on this finding, the present study explored the relationship between BP parameters and the occurrence of END. Analyzing the clinical data of 286 patients with acute ischemic stroke, 64 patients (22.3%) were found with END during hospitalization, a finding consistent with that in previous reports (18.9-25.7%) (3,21). After adjusting for confounding factors, PP parameters (24 h PP_{MEAN} and Day PP_{MEAN}) were found to be independently associated with END following ischemic stroke. BP variability parameters

Table I. Comparisons of clinical characteristics according to END.

Characteristics	No END (n=222)	END (n=64)	P-value
Age, years	64.26±11.62	63.08±10.46	0.53[a]
Male, N (%)	155 (69.82)	44 (68.75)	0.99[b]
Hypertension, N (%)	159 (71.62)	42 (65.62)	0.4[b]
Diabetic mellitus, N (%)	75 (33.78)	24 (37.50)	0.69[b]
History of stroke, N (%)	46 (20.72)	6 (9.38)	0.06[b]
Hyperlipidemia, N (%)	159 (71.62)	42 (65.62)	1.00[b]
Atrial fibrillation, N (%)	23 (10.36)	2 (3.12)	0.12[c]
Smoking, N (%)	108 (48.6)	27 (42.19)	0.44[b]
Recombinant tissue plasminogen activator therapy, n (%)	25 (11.26)	6 (9.38)	0.84[b]
Infarct location, N (%)			0.31[b]
Left hemisphere	80 (36.00)	26 (40.62)	
Right hemisphere	84 (37.83)	22 (34.38)	
Bilateral hemisphere	10 (4.50)	0 (0)	
Infratentorial	48 (21.62)	16 (25.00)	
Stroke classification, N (%)			0.11[c]
Large artery atherosclerotic stroke	111 (50)	24 (37.5)	
Small-vessel occlusion	86 (38.73)	33 (51.56)	
Cardioembolic stroke	21 (9.46)	2 (3.13)	
Other cause of stroke/stroke of unknown causes	4 (1.80)	5 (7.81)	
Anti-hypertension therapy, N (%)			0.67[c]
Without	126 (56.76)	38 (59.38)	
Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker	24 (10.81)	4 (6.25)	
β-blocker	7 (3.15)	3 (4.69)	
Calcium channel blockers	52 (23.42)	17 (26.56)	
Multiple	13 (5.86)	2 (3.12)	

END, early neurological deterioration. [a]Calculated using Mann-Whitney U test. [b]Calculated using Pearson's $\chi 2$ test. [c]Calculated using Fisher's exact test.

were more comprehensive in the present study compared with those investigated in previous studies (18-20), as in the present study the BP was monitored using continuous 24-h monitoring. Using continuous 24-h monitoring, daytime and night time blood pressure data was obtained, which provided data on blood pressure fluctuations. Compared with admission BP or daily BP measurements, 24-h ambulatory BP measurements provides insights into the BP profile of an individual and how it is associated with their daily activities (22,23). This suggests more attention should be paid to the fluctuation of PP in the early management of ischemic stroke. To obtain accurate values of blood pressure variability, each patient with ischemic stroke should complete a 24-h ambulatory blood pressure examination. A medical treatment plan centered on reducing PP and its variability is envisioned to facilitate the reduction of END occurrence.

PP is calculated using arterial systolic and diastolic pressure, which reflect the stiffness of the arterial wall (24). The predictive value of PP parameters in heart disease has been widely accepted (25,26). A number of studies have focused on the association between PP and ischemic stroke. They revealed that increases in PP within 60 h of ischemic stroke is associated with poorer short-term functional recovery and with an increased disability rate following ischemic stroke (27-31). In particular, a one-year follow-up study of 198 patients with ischemic stroke found that for every 10 mmHg increase in PP, the disability rate was increased by 40% (28). The results of the present study potentially offered further evidence that increased artery stiffness can contribute to poor automatic blood volume regulation (32,33). Therefore, PP may contribute to the development of END by altering hemodynamic status, which is vulnerable to impairment after stroke (31). However, another previous study found a non-linear reverse 'J-curve' association between the admission PP level and 3-month post-stroke functional outcomes, based on a single BP measurement upon admission (33). This finding is not consistent with that in the present study, possibly due to a number of reasons. Fluctuations in blood pressure after cerebral infarction reflect the impact on stroke more accurately (34). In addition, although 3-month post-stroke functional outcomes does appear to share a relationship with END, they can also be under the influence of other factors, such as aspiration pneumonia (35).

The use of anti-hypertensive drugs was included in the analysis of END risk factors in the present study. A number

Table II. Comparisons of blood pressure parameters according to the presence of END.

A, 24-h BP (06:00-06:00 next day)

BP parameters	No END	END	P-value
24-h SBP_{MEAN}	137.20±16.59	141.73±17.98	0.06[a]
24-h SBP_{SD}	14.20±3.97	14.51±3.5	0.4[a]
24-h SBP_{CV}	10.36±2.67	10.37±2.35	0.71[b]
24-h DBP_{MEAN}	81.07±10.64	82.22±16.46	1[a]
24-h DBP_{SD}	10.27±2.51	9.97±2.30	0.48[a]
24-h DBP_{CV}	12.79±3.15	12.90±3.21	0.27[a]
24-h PP_{MEAN}	56.13±13.50	61.05±15.67	0.03[a]
24-h PP_{SD}	9.72±3.02	10.12±2.24	0.07[a]
24-h PP_{CV}	17.51±4.07	17.01±3.46	0.31[a]

B, Daytime BP (06:00-22:00)

BP parameters	No END	END	P-value
Day SBP_{MEAN}	137.80±16.66	142.67±17.41	0.04[a]
Day SBP_{SD}	13.70±4.09	13.49±3.25	0.99[a]
Day SBP_{CV}	9.95±2.78	9.98±2.13	0.27[a]
Day DBP_{MEAN}	86.31±7.44	81.45±10.72	0.81[a]
Day DBP_{SD}	9.89±2.64	9.28±2.21	0.13[a]
Day DBP_{CV}	12.18±3.46	12.44±2.76	0.13[a]
Day PP_{MEAN}	55.95±13.09	61.23±15.11	0.01[a]
Day PP_{SD}	9.61±3.18	10.02±2.30	0.07[a]
Day PP_{CV}	17.35±4.34	16.77±3.48	0.31[a]

C, Night BP (22:00-06:00 next day)

BP parameters	No END	END	P-value
Night SBP_{MEAN}	135.79±19.43	138.17±21.89	0.56[a]
Night SBP_{SD}	12.42±4.55	13.83±5.09	0.08[a]
Night SBP_{CV}	9.23±3.35	10.19±3.93	0.13[a]
Night DBP_{MEAN}	79.09±11.42	77.63±11.78	0.61[a]
Night DBP_{SD}	9.65±3.43	9.73±3.28	0.95[a]
Night DBP_{CV}	12.36±4.46	12.81±4.62	0.71[a]
Night PP_{MEAN}	56.72±15.80	60.49±18.63	0.26[a]
Night PP_{SD}	8.49±3.17	8.94±2.78	0.16[a]
Night PP_{CV}	15.43±5.22	15.54±5.24	0.98[a]

[a]Calculated using Mann-Whitney U test. [b]Calculated using unpaired Student t-test. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; SD, standard deviation; CV, coefficient of variation.

Table III. Univariate analysis of the associations between BP parameters and the development of early neurological deterioration.

A, 24-h BP (06:00-06:00 next day)

BP parameters	OR (95% CI)[a]	P-value
24-h SBP_{MEAN}	1.02 (0.99-1.03)	0.06
24-h SBP_{SD}	1.02 (0.95-1.10)	0.57
24-h SBP_{CV}	0.99 (0.88-1.10)	0.81
24-h DBP_{MEAN}	1.01 (0.99-1.03)	0.51
24-h DBP_{SD}	0.95 (0.84-1.07)	0.39
24-h DBP_{CV}	0.96 (0.88-1.05)	0.38
24-h PP_{MEAN}	1.02 (1.00-1.04)	0.02
24-h PP_{SD}	1.05 (0.95-1.15)	0.34
24-h PP_{CV}	0.97 (0.89-1.04)	0.37

B, Daytime BP (06:00-22:00)

BP parameters	OR (95% CI)[a]	P-value
Day SBP_{MEAN}	1.02 (1.00-1.03)	0.04
Day SBP_{SD}	0.99 (0.92-1.06)	0.7
Day SBP_{CV}	0.93 (0.82-1.04)	0.2
Day DBP_{MEAN}	0.99 (0.97-1.00)	0.68
Day DBP_{SD}	0.91 (0.80-1.01)	0.09
Day DBP_{CV}	0.93 (0.85-1.02)	0.12
Day PP_{MEAN}	1.03 (1.01-1.05)	0.01
Day PP_{SD}	1.04 (0.95-1.14)	0.35
Day PP_{CV}	0.96 (0.89-1.03)	0.32

C, Night BP (22:00-06:00 next day)

BP parameters	OR (95% CI)[a]	P-value
Night SBP_{MEAN}	1.01 (0.99-1.02)	0.42
Night SBP_{SD}	1.06 (1.00-1.13)	0.04
Night SBP_{CV}	1.08 (0.99-1.17)	0.06
Night DBP_{MEAN}	0.99 (0.96-1.01)	0.39
Night DBP_{SD}	1.00 (0.92-1.10)	0.87
Night DBP_{CV}	1.02 (0.96-1.09)	0.5
Night PP_{MEAN}	1.01 (0.99-1.03)	0.12
Night PP_{SD}	1.05 (0.95-1.15)	0.32
Night PP_{CV}	1.00 (0.95-1.06)	0.89

[a]ORs and their CIs were obtained by univariate logistic regression analysis. OR, odds ratio; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; SD, standard deviation; CV, coefficient of variation.

of previous studies have suggested that the BP control strategy used during the acute period of ischemic stroke has considerable impact on disease prognosis (36,37). In particular, calcium channel blockers or β-receptor blockers are recommended, because they can reduce BP level and variability (38). However, the present study did not find an association between various types of anti-hypertensive drugs and END. A possible reason for this is that the number of patients in the anti-hypertensive drug group was insufficient to demonstrate efficacy. In future studies, larger clinical studies are needed to confirm this possible association.

Table IV. Multivariable analysis of the associations between variables and the development of early neurological deterioration.

Characteristics	Adjusted OR (95% CI)[a]	P-value
Age	0.98 (0.95-1.01)	0.22
History of stroke	0.29 (0.10-0.74)	0.02
Atrial fibrillation	0.19 (0.01-1.15)	0.14
Stroke classification	1.73 (0.88-3.45)	0.11
24-h PP_{MEAN}	1.08 (1.01-1.16)	0.02
Day PP_{MEAN}	1.20 (1.011-1.45)	0.04
Night SBP_{SD}	0.86 (0.72-1.02)	0.08

[a]ORs and their CIs were obtained by multiple logistic regression analysis, adjusted for age, history of stroke, atrial fibrillation and stroke classification. OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.

The relationship of BP variability with END is controversial according to previous studies (39,40). PP is considered a stable parameter that can reflect the impact of BP fluctuations on cerebral blood flow perfusion (41). It is considered that higher PP could transmit excessive pulsatile force into the cerebral microcirculation leading to microvascular damage and regional hypoperfusion (42). Recently, a study found that persistently high PP in acute ischemic stroke is a predictor of neurological deterioration (42). This conclusion strongly supported the results of the present study, which will contribute to the prediction of END onset in patients with stroke (43). However, attention should be paid to patients with ischemic stroke with high PP during the acute stages.

The present study has several limitations. The present is a single-center study with a limited sample size. Findings from the present study must be verified by multicenter studies with larger sample sizes. In addition, imaging data of post-END was not included in the present analysis. Various studies have previously found that a history of diabetes mellitus is associated with END (44,45). However, a number of studies have also failed to find a relationship between diabetes mellitus and END (46,47). In the present study, a higher proportion of diabetes mellitus was found in the END group compared with that in the no-END group. The small sample size of the present study may partly explain this discrepancy.

In conclusion, the present study demonstrates that PP variations (24-h PP_{MEAN} and Day PP_{MEAN}) in patients with acute ischemic stroke is independently associated with the occurrence of END. Therefore, a PP-based strategy should be developed for the management of patients with ischemic stroke to reduce the occurrence of END. Patients with a high PP must be especially identified before admission and treatment in a clinical setting.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PL acquired, analyzed clinical data and drafted the manuscript. LWZ analyzed clinical data and drafted the manuscript. XC designed the study and revised the manuscript. PL and XC confirm the authenticity of all the raw data. All authors contributed to the article, and read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics review board of China-Japan friendship hospital (approval no. 2020-90-K55) and was conducted in accordance with the institutional guidelines. Written informed consent was provided by all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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