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Effect of morning blood pressure peak on early progressive ischemic stroke: a prospective clinical study

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ABSTRACT

Objective: To prospectively evaluate the effect of morning blood pressure peak (MBPP) on early progressive ischemic stroke (EPIS).

Patients and Methods: A total of 135 patients with acute ischemic stroke were enrolled and completed all assessments. The patients were divided into EPIS group and non-EPIS group, with 22 and 113 cases in each group, respectively, according to the assessment of Scandinavian stroke scale within three days after onset. All cases received conventional treatment for stroke and its risk factors. 24 -h dynamic blood pressure monitoring was performed within 24 h after admission. Based on the 24 -h mean blood pressure, MBPP, morning blood pressure, and other risk factors for EPIS, we conducted a logistic regression analysis to evaluate whether MBPP was an independent risk factor for EPIS.

Results: Mean systolic blood pressure, systolic and diastolic MBPP, morning systolic and diastolic blood pressure were all significantly higher in EPIS group than in non-EPIS group ($p = 0.037$, $p = 0.001$, $p = 0.035$, $p = 0.003$, $p = 0.042$, respectively). Logistic regression analysis showed that MBPP was an independent risk factor for EPIS ($OR = 1.057$, 95% CI 1.014–1.102, $p = 0.009$). Further stratified analysis showed that incidences of EPIS in patients with elevated MBPP combined with large artery atherosclerosis or small artery occlusion were comparable (41.2% vs. 25.0%, $p = 0.367$), and the systolic MBPP was significantly higher in morning EPIS group than in non-morning EPIS group ($p = 0.041$).

Conclusion: Elevated systolic MBPP might be an independent risk factor for EPIS, and play a more obvious effect on EPIS manifesting in the morning especially.

1. Introduction

Ischemic stroke is a serious disease worldwide leading to death and disability [1], especially progressive ischemic stroke (PIS) [2]. PIS is a phenomenon that the neurological deficit is relatively mild after the onset, but gradually aggravates until serious neurological deficit appear in one week [2]. The incidence rate of PIS was reported to reach 9.8–43.0%, and early progressive ischemic stroke (EPIS), which occurred within three days after onset, affected the prognosis of stroke [3]. Thus, identifying the risk factors of EPIS and early intervention were very important for improving the prognosis. Blood pressure variability, especially the morning blood pressure peak (MBPP), has been confirmed to be associated with ischemic stroke [4,5]. However, the relationship between MBPP and EPIS remains unknown. In this study, we prospectively evaluated the effect of MBPP on EPIS via multifactor analysis, in order to explore more potential intervention targets for preventing EPIS.

2. Materials and methods

2.1. Patients

Inclusion criteria: (1) ischemic stroke diagnosis was based on the World Health Organization criteria [6]; (2) hospitalized within 24 h after onset; (3) initial stroke; (4) more than 18 years; (5) signed informed consent provided by the patients or their legal relatives.

Abbreviation: MBPP, Morning blood pressure peak; EPIS, early progressive ischemic stroke

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Exclusion criteria: (1) hemorrhagic stroke; (2) disturbance of consciousness; (3) an exact previous history of ischemic stroke; (4) uncertain etiology; (5) somnipathy; (6) poor coordination on 24 -h dynamic blood pressure monitoring; (7) neurological deficits aggravated before the 24 -h dynamic blood pressure monitoring was performed; (8)participating in other clinical studies.

2.2. Grouping

On admission, the enrolled patients were assessed based on the Scandinavian stroke scale (SSS), which was repeated if any neurological deficits aggravated within three days after onset. According to the diagnostic criteria for EPIS by the European progressive stroke research group, any two consecutive SSS assessments were performed within three days after onset, and EPIS was considered based on the following criteria: assessments of upper limb movement, lower limb movement, eye movement, or consciousness level ≥ 2 points, or language function ≥ 3 points [7]. Then, the enrolled patients were divided into EPIS group and non-EPIS group. Furthermore, according to whether the stroke was progressive in the morning time (from 6:00 to 10:00 AM) or during sleep and manifested immediately after wake-up, the enrolled patients in the EPIS group were divided into morning EPIS group and non-morning EPIS group.

2.3. Dynamic blood pressure monitoring

24 -h dynamic blood pressure monitoring was performed for all patients within 24 h after enrollment, using a portable dynamic blood pressure monitor (model number: ABPM-6100, made by USA Wellen company). The monitoring time was from nearest 12:00 AM to 12:00 AM next day, while the frequency of blood pressure measurement was set for every half an hour. The wake-up time of patients in the morning was recorded, and strenuous exercise was forbidden during the monitoring. The value of MBPP, 24 -h mean blood pressure and morning blood pressure were calculated according to the dynamic blood pressure monitoring. MBPP = (mean blood pressure within two hours after wake-up in the morning)–(mean blood pressure for the one hour including the lowest value at night) [8]; More than 35 mmHg was considered as the standard for elevated systolic MBPP [8]; morning blood pressure = mean blood pressure within two hours after wake-up in the morning [9]. If the patient failed to wake up in the morning due to illness, the mean blood pressure between 6:00 AM and 10:00 AM was used to represent the morning blood pressure [9]. The systolic and diastolic MBPP were the primary observing indicators.

2.4. Other observation indicators

Age, gender, time of starting treatment after onset, Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification [10], whether receiving intravenous thrombolysis or thrombectomy, whether treated with antihypertensive or hypoglycemic drugs, and any existing pulmonary or urinary tract infection within three days after onset were recorded. TOAST classification in this study included large artery atherosclerosis (LAA), small artery occlusion (SAO), Cardiogenic embolism (CE) and stroke of other demonstrated etiology (SOE). Undetermined etiology was excluded at admission since stroke of uncertain etiology might affect stratification analysis. Plasma fibrinogen and low-density lipoprotein cholesterol (LDL-C) examination, carotid color doppler ultrasound, electrocardiogram, head magnetic resonance imaging and angiography were conducted. LDL-C > 4.24 mmol/L was considered as high low-density lipoproteinemia [11].

2.5. Sample size estimation

We used the data of first 30 cases enrolled in our study for total sample size estimation. In these cases, 6 patients suffered with EPIS and 24 patients didn't, as the systolic MBPP were 27.10 ± 7.41 mmHg and 14.26 ± 11.09 mmHg respectively. With type I error alpha set at 0.05, type II error beta at 0.20, test power at 80%, the sample size needed should be 134 cases as calculated by the *PASS 11.0 software* (NCSS, United State). The expected shedding ratio at about 10%, thus the total sample size was 148 cases.

2.6. Blinding

In this study, evaluator-blinding was adapted. Dynamic blood pressure monitoring was conducted by a specialized inspector, SSS assessment was performed by a specialized neurologist, and all the data was recorded by a specialized recorder. The above personnel were forbidden to participate in the treatment and statistical analysis of this study. The treatment of all enrolled patients was conducted by the same neurology team, which was not involved in the processes of record and assessment. Statistical analysis was performed by a dedicated senior statistician, who was not involved in other processes of the study.

2.7. Treatment

Treatments for ischemic stroke, PIS and other risk factors for cerebral vascular disease were based on the *Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack* formulated by the American Heart Association and the American Stroke Association [12]. The initial target was 120–140 mmHg for systolic blood pressure and 70–90 mmHg for diastolic blood pressure. All enrolled cases received the same rehabilitation treatment and health education.

2.8. Ethical standard

This study was approved by the Shenzhen People's Hospital Ethics Committee. Patients or their legal relatives were explained the purpose, significance and possible risks of the study, and requested to sign informed consent before enrollment. Furthermore, they had the right to withdraw after enrollment.

2.9. Statistics

SPSS 24.0 was used for statistical analysis. Measurement data with normal distribution was presented as mean ± standard deviation (SD), and compared by *t*-test. Measurement data with skewed distribution was presented as median and quartile, and compared by *rank sum* test. *Chi-square* test was used to assess count data. Logistic regression analysis was used to evaluate whether MBPP was an independent risk factor for EPIS. Result was considered to be significant at $p < 0.05$.

3. Results

The roadmap of this study was showed as Fig. 1. A total of 148 cases with acute ischemic stroke who met the inclusion criteria were consecutively enrolled into this study from January 2016 to December 2017 in the department of neurology, Shenzhen People's Hospital, China. Among them, 13 cases were lost before completion of all assessments, with a shedding rate of 8.8%, and a total of 135 cases were finally enrolled for the statistical analysis. These patients were divided into the EPIS group with 22 cases and the non-EPIS group with 113 cases according to SSS assessment within three days after onset. The incidence rate of EPIS was 16.3% in our study. Age, proportion of males, TOAST classifications, time of starting treatment after onset, proportions of patients receiving intravenous thrombolysis and thrombectomy, proportions of patients with atrial fibrillation, and SSS assessment at baseline were comparable between the two groups. The proportions of carotid or intracranial artery stenosis > 50% and existing carotid unstable plaque were significantly higher in the EPIS group than in the non-EPIS group (45.5% vs. 16.8%, $p = 0.003$; 50.0%

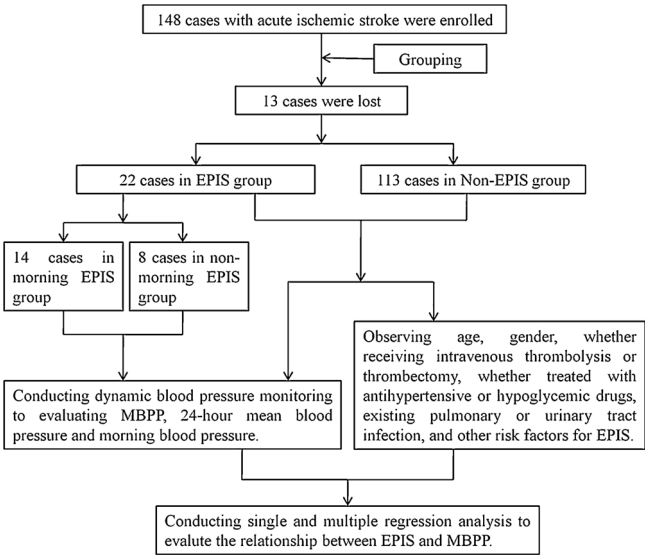

Fig. 1. Roadmap of study.

vs. 20.4%, $p = 0.003$, respectively). The proportions of hypertension, diabetes, pulmonary or urinary tract infection were all significantly higher in the EPIS group than in the non-EPIS group (81.8% vs. 58.4%, $p = 0.038$; 36.4% vs. 15.0%, $p = 0.019$; 22.7% vs. 7.1%, $p = 0.023$, respectively). The proportion of hypertensive patients taking antihypertensive drugs was comparable between the two groups, both for combination and single drug therapy. The proportion of diabetic patients taking hypoglycemic therapy was comparable between the two groups, both for oral hypoglycemic drugs or insulin alone and combination therapy. There was no significant difference between the two groups in the proportion of high low-density lipoproteinemia and the plasma fibrinogen levels (Table 1).

The mean systolic blood pressure was significantly higher in the EPIS group than in the non-EPIS group ($p = 0.037$), but the mean diastolic pressure was comparable between the two groups. The systolic and diastolic MBPP in the EPIS group were significantly higher than in the non-EPIS group ($p = 0.001$, $p = 0.035$, respectively). The morning systolic and diastolic blood pressure in the EPIS group were significantly higher than in the non-EPIS group ($p = 0.003$, $p = 0.042$, respectively) (Table 2 and Fig. 2).

Binary logistic regression analysis was conducted using the indicators with statistical significance in the single-factor analysis as independent variables, such as existing carotid unstable plaque, carotid or intracranial artery stenosis > 50%, mean systolic pressure, systolic and diastolic MBPP, morning systolic and diastolic blood pressure, diabetes, and pulmonary or urinary tract infection, and existing EPIS as the dependent variable. It showed that existing carotid unstable plaque, carotid or intracranial artery stenosis > 50%, mean systolic pressure, pulmonary or urinary tract infection and systolic MBPP were independent risk factors for EPIS, while the *OR* was 1.057 for systolic MBPP (95% *CI* 1.014–1.102, $p = 0.009$) (Table 3).

The incidence of EPIS was not significantly different between the patients with elevated systolic MBPP combined with LAA or SAO ischemic stroke (41.2% vs. 25.0%, $p = 0.367$) (Table 4).

There were 14 cases in morning EPIS group and 8 cases in non-morning EPIS group. The systolic MBPP was significantly higher in the morning EPIS group than in the non-morning EPIS group ($p = 0.041$), while the mean systolic and diastolic pressure, diastolic MBPP, morning systolic and diastolic blood pressure were comparable between the two groups (Table 5).

4. Discussion

MBPP refers to the clinical phenomenon wherein the blood pressure rapidly rises from a relatively low level to high level in the morning [8]. While the effect of absolute blood pressure value is usually monitored, the effect of blood pressure variability, especially MBPP on EPIS, is largely ignored. However, ischemic stroke and early aggravation typically occur in the morning [13]. EPIS greatly influences the prognosis of

Table 1
Comparison of baseline data between EPIS group and non-EPIS group.

	EPIS group	Non-EPIS group	*t* or X^2 value	*p* value
Number of case (n)	22	113		
Age (year)	65.68 ± 12.52	61.58 ± 12.02	−1.457★	0.148
Male (n, %)	16 (72.7%)	91 (80.5%)	0.682☆	0.409
Time starting treatment after onset (hour)	15.07 ± 7.17	14.48 ± 7.22	−0.351★	0.726
Receiving intravenous thrombolysis (n, %)	2 (9.1%)	9 (8.0%)	0.031☆	0.860
Receiving thrombectomy (n, %)	1 (4.4%)	5 (4.5%)	0.001☆	0.980
TOAST classification: LAA/SAO/CE/SOE (n, %)	14/6/2/0 (63.6%/27.3%/9.1%/0%)	61/43/4/5 (54.0%/38.1%/3.5%/4.4%)	0.927☆	0.629
SSS score at baseline	29.82 ± 5.65	28.85 ± 4.96	−0.819★	0.414
Carotid or intracranial artery stenosis > 50% (n,%)	10 (45.5%)	19 (16.8%)	8.955☆	***0.003***
Carotid unstable plaque (n, %)	11 (50.0%)	23 (20.4%)	8.589☆	***0.003***
Atrial fibrillation (n, %)	2 (9.1%)	4 (3.5%)	1.336☆	0.248
Hypertension (n, %)	18 (81.8%)	66 (58.4%)	4.294☆	***0.038***
Using antihypertensive drugs for hypertension (n, %) ◎	9 (50.0%)	43 (65.2%)	1.377☆	0.241
Only using CCB for hypertension (n, %)∞	4 (44.4%)	22 (51.2%)	0.134☆	0.714
Only using ACEI for hypertension (n, %)∞	2 (22.2%)	11 (25.6%)	0.045☆	0.832
Only using ARB for hypertension (n, %)∞	1 (11.1%)	4 (9.3%)	0.028☆	0.867
Using two or more drugs for hypertension (n, %)	2 (22.2%)	6 (14.0%)	0.391☆	0.532
Diabetes (n, %)	8 (36.4%)	17 (15.0%)	5.547☆	***0.019***
Using hypoglycemic therapy for diabetes (n, %) ◎	7 (87.5%)	14 (82.4%)	0.107☆	0.743
Only using oral hypoglycemic drug for diabetes (n, %)∞	4 (57.1%)	6 (42.9%)	0.382☆	0.537
Only using insulin for diabetes (n, %)∞	2 (28.6%)	5 (35.7%)	0.107☆	0.743
Combination of oral drug and insulin for diabetes (n, %)	1 (14.3%)	3 (21.4%)	0.154☆	0.694
High low density lipoproteinemia (n, %)	6 (27.3%)	26 (23.0%)	0.185☆	0.667
Plasma fibrinogen (g/L)	3.02 ± 0.73	3.10 ± 0.92	0.351★	0.726
Acute pulmonary or urinary tract infection (n, %)	5 (22.7%)	8 (7.1%)	5.181☆	***0.023***

Note: n: number of case. CCB: calcium channel blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker. ★Conducted *t* test. ☆ Conducted chi-squared test. ◎The percentage represented proportion of patients with hypertension or diabetes treated with antihypertensive or hypoglycemic therapy. ∞ The percentage represented proportion of patients receiving antihypertensive or hypoglycemic therapy treated with the assigned antihypertensive or hypoglycemic therapy.

Table 2
Comparisons of the mean blood pressure, MBPP, morning blood pressure between EPIS group and non-EPIS group.

	EPIS group	Non-EPIS group	*t* value	*p* value
Number of case (n)	22	113		
Mean systolic blood pressure (mmHg)	147.82 ± 22.01	136.93 ± 16.58	−2.202	***0.037***
Mean diastolic blood pressure (mmHg)	84.00 ± 14.62	80.08 ± 8.51	−1.218	0.235
Systolic MBPP (mmHg)	27.79 ± 15.37	16.89 ± 12.86	−3.520	***0.001***
Diastolic MBPP (mmHg)	15.61 ± 10.47	10.87 ± 9.35	−2.133	***0.035***
Morning systolic blood pressure (mmHg)	153.58 ± 20.10	140.51 ± 17.86	−3.051	***0.003***
Morning diastolic blood pressure (mmHg)	90.15 ± 14.54	83.22 ± 9.83	−2.142	***0.042***

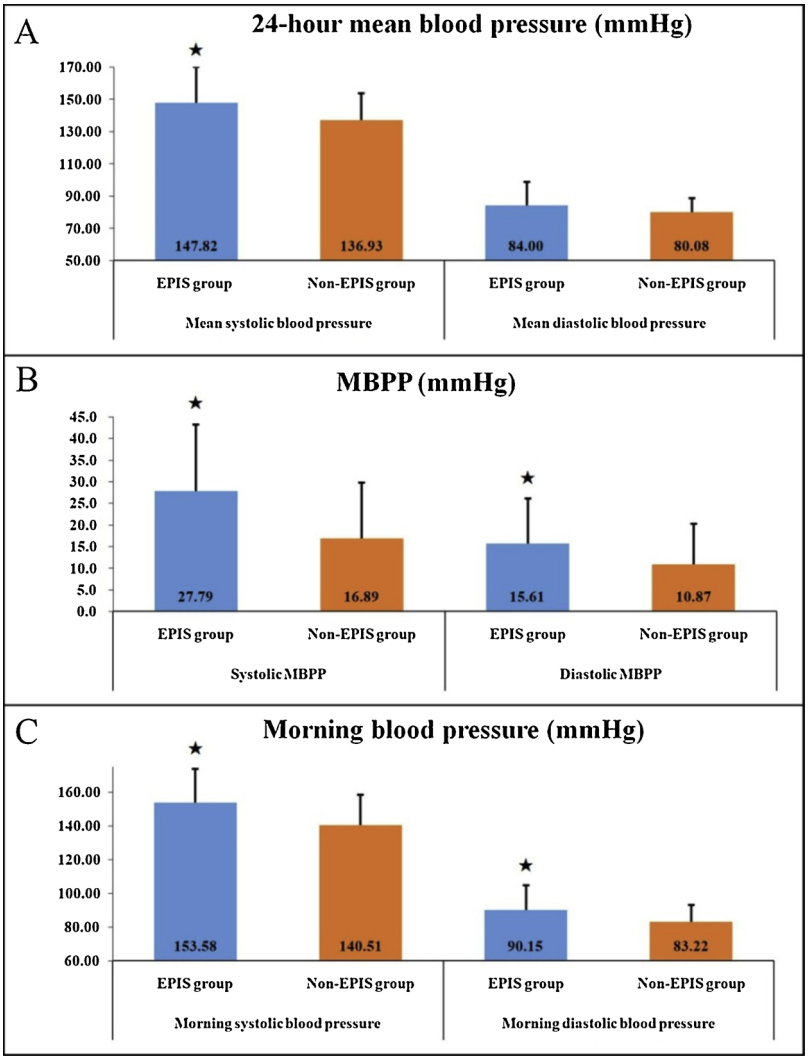

Fig. 2. Comparisons of the mean blood pressure, MBPP, morning blood pressure between EPIS group and non-EPIS group.
Note: ★ represented that the valve in EPIS group was significant higher than non-EPIS group ($p < 0.05$)

stroke, but some of its etiological mechanisms remain unclear, such as any correlation between MBPP and EPIS. Thus, evaluating the relationship between MBPP and EPIS, and exploring new target for preventing EPIS were meaningful.

Recent studies suggested that MBPP was a predictive factor for ischemic stroke, and independent of 24 -h mean blood pressure [14,15]. However, the effect of MBPP on EPIS has not yet been reported. In this study, mean systolic blood pressure, systolic and diastolic MBPP, morning systolic and diastolic blood pressures were significantly higher in the EPIS group than in the non-EPIS group. Based on the other risk factors of EPIS, further regression analysis showed that systolic MBPP was an independent risk factor for EPIS. We speculate several potential mechanisms for MBPP affecting EPIS. First, the elevated MBPP, especially systolic MBPP, is an important manifestation of elevated blood pressure variability [16]. The obvious fluctuation of blood pressure can lead to hemodynamic changes, and result in a sudden increasing pressure gradient on the inner wall of carotid artery, that will form shear force on the arterial wall [16]. This sudden shear force on arterial wall will tear the originally stable plaques to form ulcerative plaques [16], which may lead to progressive carotid stenosis or thrombosis. Second, elevated MBPP could enhance the activity of ubiquitin proteinase in carotid atherosclerotic lesions, which could increase plaque instability and induce plaque rupture [17]. In addition, the sudden hemodynamic changes caused by elevated MBPP will lead to high-speed turbulence at

Table 3
Binary Logistic regression analysis of the risk factors for EPIS (final result).

	B	*SE*	*Wald*	*df*	*p* value	*Exp (B)*	*95% CI*
Constant	−9.619	2.579	13.915	1			
Carotid unstable plaque	1.357	0.609	4.962	1	***0.026***	3.884	1.177 ~ 12.819
Carotid or intracranial artery stenosis > 50%	1.918	0.653	8.626	1	***0.003***	6.807	1.893 ~ 24.479
Mean systolic blood pressure	0.039	0.017	5.288	1	***0.021***	1.039	1.006 ~ 1.074
Systolic MBPP	0.055	0.021	6.801	1	***0.009***	1.057	1.014 ~ 1.102
Acute pulmonary or urinary tract infection	1.665	0.817	4.154	1	***0.042***	5.286	1.066 ~ 26.214

Note: conducted binary Logistic regression analysis (forward Wald method). Whether existing EPIS was used as dependent variable, while carotid unstable plaque, carotid or intracranial artery stenosis more than 50%, mean systolic pressure, systolic and diastolic MBPP, morning systolic and diastolic blood pressure, diabetes, and pulmonary or urinary tract infection were used as independent variables.

the bifurcation of carotid artery [18], which might induce the rupture or shedding of the unstable plaque, and eventually lead to arterial embolization. Additionally, the shear force on artery wall formed by elevated MBPP could induce vasospasm [19], which might worsen cerebral ischemia. Furthermore, elevated MBPP increased blood viscosity in the morning [18,20], and damaged the endothelial function of vessel [18], all of which can worsen cerebral ischemia. Finally, elevated MBPP could increase the activity of inflammatory factors, such as tumor necrosis factor, interleukin-1 and interleukin-6 [21], which can increase injury of brain tissue and instability of carotid plaque in acute ischemic stroke [21].

In this study, although the incidences of EPIS were comparable between patients with elevated systolic MBPP combined with LAA or SAO, the former had a higher tendency. This result suggested that the effect of systolic MBPP on large cerebral artery might be more obvious than on small artery. We speculated that the effect of elevated systolic MBPP on the intracranial and external vessels of patients with ischemic stroke mainly reflected in the injury on vascular endothelium or plaque caused by the intravascular shear force, thus MBPP might have more obvious effects on the large arteries. However, the number of cases was limited after stratified analysis, so the statistical results might be biased, and needed further well-designed studies for confirmation.

This study indicated that systolic MBPP was significantly higher in patients with EPIS manifesting in the morning than in non-morning time. This result confirmed that systolic MBPP might play a more important role on EPIS manifesting in the morning. Hence, we should pay close attention to whether systolic MBPP is elevated during EPIS manifesting in morning time.

In this study, diastolic MBPP was not an independent factor affecting EPIS. Systolic blood pressure was previously shown to be more relevant for the adverse effect on intracranial and extracranial arteries than diastolic blood pressure [22]. Thus, the negative effect of systolic MBPP on EPIS might also be greater than diastolic MBPP.

A previous study showed that morning blood pressure was a risk factor for ischemic stroke, and suggested that monitoring morning blood pressure instead of 24 -h dynamic blood pressure was a more convenient method to evaluate the control of blood pressure, since morning blood pressure was easier to monitor at home [23]. However, the effect of morning blood pressure and MBPP on ischemia or EPIS has not been previously compared. In this study, although morning systolic and diastolic blood pressure were significantly higher in patients with EPIS, multi-factor analysis showed that morning blood pressure had no significant effect on EPIS, while MBPP was an independent risk factor for EPIS. This result suggested that the effect of MBPP on EPIS might be more obvious than the absolute value of morning blood pressure. Since most patients of EPIS are hospitalized, it is easy to perform 24 -h dynamic blood pressure monitoring. Thus, assessment of MBPP should be recommended for the prevention and treatment of EPIS.

This study had some limitations. First, for the inclusion and exclusion criteria were strict, the collection of cases was relatively difficult and the sample size was not large, especially for the EPIS group and stratified analysis. Second, multicollinearity might exist between independent variables in multi-factor regression analysis. Third, it was difficult to assess the SSS score from onset to enrollment, although the time would not exceed 24 h. Finally, although we conducted dynamic blood pressure monitoring as quickly as possible after enrollment, and excluded the cases whose neurological deficits aggravated obviously before the 24 -h dynamic blood pressure monitoring was performed, the effect of PIS on fluctuation of blood pressure could not be completely excluded in our study. The above limitations might lead to certain biases in the results, and reduce the demonstrate strength of the conclusion.

5. Conclusion

Elevated systolic MBPP might be an independent risk factor for EPIS, and play a more obvious effect on EPIS manifesting in the morning especially. The main mechanisms might be inducing intravascular shear force and vasospasm, increasing the blood viscosity, and promoting the secretion of inflammatory factors. The effect of systolic MBPP on EPIS might be more obvious than morning blood pressure. Therefore, for inpatients with ischemic stroke, it is recommended to conduct 24 -h dynamic blood pressure monitoring in order to detect elevated MBPP early, so that targeted anti-hypertension treatment could be performed for preventing EPIS.

Funding and registration

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Table 4
Comparison of EPIS between patients of elevated systolic MBPP combined with LAA and SAO ischemic stroke.

	Patients of elevated systolic MBPP combined with LAA ischemic stroke	Patients of elevated systolic MBPP combined with SAO ischemic stroke	*X2* value	*p* value
Number of case (n)	17	12		
Occurring EPIS (n, %)	7 (41.2%)	3 (25.0%)	0.815	0.367

Table 5
Comparisons of the mean blood pressure, MBPP, morning blood pressure between morning EPIS group and non-morning EPIS group.

	Morning EPIS group	Non-morning EPIS group	*t* value	*p* value
Number of case (n)	14	8		
Systolic MBPP (mmHg)	32.77 ± 16.30	19.09 ± 8.93	−2.179	***0.041***
Diastolic MBPP (mmHg)	17.18 ± 11.38	12.87 ± 8.66	−0.925	0.366
Mean systolic blood pressure (mmHg)	144.29 ± 21.87	154.00 ± 22.29	0.835	0.331
Mean diastolic blood pressure (mmHg)	81.57 ± 14.63	88.25 ± 14.54	1.032	0.314
Morning systolic blood pressure (mmHg)	153.46 ± 21.70	153.80 ± 21.16	0.036	0.972
Morning diastolic blood pressure (mmHg)	90.63 ± 15.74	89.33 ± 13.17	−0.198	0.845

Conflicts of interest

The authors declare that they have no conflicts of interest in this work.

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