Effect of blood pressure variability on early neurological deterioration in single small subcortical infarction with parental arterial disease

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ABSTRACT

Background and purpose: Early neurological deterioration (END) is not uncommon in acute single small subcortical infarct (SSSI), especially in those with parental arterial disease (PAD). The purpose of this study was to elucidate the effect of BP variability on the development of END as well as functional outcome at 90 days in SSSI and to determine whether the effect is linked to the status of parent artery.

Methods: Consecutive patients with acute SSSI were prospectively recruited from the First People’s Hospital of Yangzhou between Aug 2013 and Jul 2016. END was defined as a NIHSS score increased ≥ 2 during the first 72 h compared with the initial NIHSS score. Functional outcome at 90 days after onset was assessed using the modified Rankin Score (mRS) and dichotomized as good (0–2) and poor (≥ 3). During this period, the parameters of BP variability such as BPmax-min, BPSD, and BPCV (equal to [SD × 100] / mean) were calculated.

Results: A total of 296 patients were included in the analysis. Of these, 30 (38.5%) SSSI associated with PAD and 53 (24.3%) without developed END respectively. Logistic regression analysis demonstrated that SBPmax (OR 1.032, 95% CI 1.003–1.061), SBPmin (OR 1.041, 95% CI 1.006–1.078), SBPmean (OR 1.034, 95% CI 1.001–1.069), SBPv (OR 1.018, 95% CI 1.002–1.034), DBPmax (OR 1.022, 95% CI 1.000–1.045), DBPmin (OR 1.007, 95% CI 1.000–1.014), DBPmean (OR 1.016, 95% CI 1.005–1.028), DBPv (OR 1.019, 95% CI 1.002–1.035), SBPcv (OR 1.306, 95% CI 1.049–1.626), DBPcv (OR 1.369, 95% CI 1.032–1.816), and BPCV (OR 1.596, 95% CI 1.281–1.997) were all the independent predictors of END after acute SSSI associated with PAD. However, for those without PAD, none of the BP parameters was found significantly associated with END. Also, BP parameters were not related to the poor outcome at 90 days after onset.

Conclusions: Our study demonstrated that the acute in-hospital BP variability was associated with the development of END in patients with acute SSSI. However, its impact varies depending on the status of parent artery. Neither evidence-based nor consensus-based guidelines exist recommending how to prevent or halt END [6]. Efforts have been made to establish presentation features that may help identifying patients at risk of deterioration [6–12]. Currently, hemodynamic factors have been proposed as one of possible mechanisms of progression after acute stroke [13,14]. As one of the hemodynamic factors, blood pressure (BP) variability was reported to be associated with vascular events, poor functional outcome and death during long-term follow-up [15,16]. There were also studies on the association between BP variability and early edema, lesion growth, symptomatic hemorrhagic transformation after acute stroke treated with thrombolytic agent [17–19]. Thus, we hypothesized that the BP variability might be associated with END as well as poor outcome at 90 days after acute SSSIPAD.

The purpose of this study was to elucidate the effect of acute in-hospital BP variability on the development of END and poor outcome at...
90 days after onset in patients with acute SSSI and to determine whether the effect is linked to the status of parent artery.

2. Subjects and methods

2.1. Patient selection

Between Aug 2013 and Jul 2016, consecutive patients with acute ischemic stroke were prospectively registered from the First People’s Hospital of Yangzhou. Patients were enrolled into our study if they fulfilled the inclusion criteria: (1) age older 18 years, (2) time from symptom onset to admission of 24 h or less, (3) magnetic resonance imaging (MRI) performed within 24 h after admission; (4) acute isolated infarction in the perforator territory of the MCA, (5) the largest diameter of lesion on axial diffusion-weighted imaging (DWI) ≤ 20 mm. We excluded patients who met the following criteria: (1) history of stroke, (2) patients with potential cardiac embolic sources, (3) treated with thrombolytic agents and interventional therapy, (4) significant stenosis (≥ 50%) in responsible extracranial large artery, (5) early discharge or had inadequate BP data, defined as BP measured fewer than 30 times during the first 72 h. The study was approved by Ethics Committees of the First People’s Hospital of Yangzhou and written informed consent was obtained from each patient.

3. Clinical assessment and treatment

Detailed demographic, clinical and laboratory parameters were recorded and analyzed in our study. Hypertension was defined as blood pressure ≥ 140/90 mm Hg, or use of antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose ≥ 126 mg/dl, positive ≥ 75 g oral glucose tolerance test result, or use of insulin or oral hypoglycemic agents. Hyperlipidemia was defined as a serum total cholesterol level ≥ 240 mg/dl, or use of cholesterol-reducing medications. Current cigarette smoking was defined as current or quit smoking ≤ 6 months prior. Drinking was defined as intake > 80 g/day or quit drinking ≤ 6 months prior. Hypertension, diabetes, hyperlipidemia, smoking, drinking and ischemic heart disease were defined as stroke risk factors.

Once patients had been admitted to the stroke unit, antithrombotic therapies (including mono-antiplatelet or dual antiplatelet therapy), stain and management of blood pressure, glucose, and lipids were carried out based on the stroke unit’s therapeutic and diagnostic protocol [20]. Clinical status was assessed using the National Institutes of Health Stroke Scale (NIHSS) at admission and continued at the following 72 h 1–3 times a day. END was defined as an NIHSS score increased by 2 or more points during the first 72 h compared with the initial NIHSS score [17,21,22]. The functional outcome at 90 days after onset was noted as the modified Rankin Score (mRS), which was dichotomized as good (0–2) and poor (≥ 3). The evaluation of END and the functional outcome was conducted by certificated investigators who were blinded to the clinical features.

3.1. Imaging analysis

According to our imaging protocol, all patients underwent an MRI scanning during the first 24 h after admission with 1.5-T (Signa; GE, Fairfield, CT, USA) or 3.0-T (Magnetom Avanto; Siemens, Munich, Germany) MRI largely depending on which one was available to achieve a quick evaluation. The imaging protocol included T1-weighted imaging, T2-weighted imaging, DWI, fluid-attenuated inversion recovery (FLAIR), and 3D time-of-flight magnetic resonance angiography (MRA). The diagnosis of infarcts on the MCA perforating territory was made with the use of a previously published template [23]. The size of the infarction was also analyzed and represented by the largest diameter of the lesion on DWI. Severity of white matter hyperintensity (WMH) (assessed according to the grading scales reported by Fazekas) was also evaluated and detailed documented from the MRI imaging and the deep white matter hyperintensities with scores of 2 and 3 were considered to be significant WWMH in this study [24].

The status of the parent artery was evaluated using either MRA or computed tomographic angiography (CTA) and categorized as normal, mild (< 50%) stenosis, and moderate to severe (≥ 50% to occlusion) stenosis. In our study, stenosis of any degree was regarded as a significant cause of SSSI. According to the status of parent artery, two patterns of SSSI were shown: SSSI associated with PAD and those without (as shown in Figs. 1 and 2). Concomitant intracranial atherosclerotic stenosis (ICAS) and extracranial atherosclerotic stenosis (ECAS) that unrelated to the new SSSI were also evaluated according to WASID criteria and NASCET criteria, respectively [25,26]. The presence and the degree of cerebrocervical artery stenosis were analyzed by consensus among two physicians who were blinded to clinical status and the interrater variability (κ) was 0.89 for the identification of the artery status.

3.2. BP measurements and management

For each patient, systolic BP (SBP) and diastolic BP (DBP) were measured fewer than 30 times during the course. Diastolic hypertension was defined as blood pressure ≥ 126 mg/dl, and the degree of cerebrocervical artery stenosis were analyzed by consensus among two physicians who were blinded to clinical status and the interrater variability (κ) was 0.89 for the identification of the artery status.

Fig. 1. Example of SSSIPAD: a 67 years old man, END was occurred during the first 17 h after onset.
assessed during the first 72 h after admission. In general wards, BP was measured in the nonparalyzed arm using a standard mercury sphygmomanometer. In the stroke unit or intensive care unit, BP was measured using a noninvasive BP monitoring device and recorded automatically into the electronic medical record. For each patient, BP was measured > 40 times during the first 72 h after admission.

The BP profile during the first 72 h was described using various parameters for each of SBP and DBP: the mean (an average of values

![Figure 2](image_url)

Fig. 2. Example of SSSI without PAD: a 73 years old woman, whose clinical condition had not get worse during the first 72 h after onset.

| Characteristics                      | SSSI with PAD | SSSI without PAD |
|---------------------------------------|---------------|------------------|
| Age, years, mean (SD)                | 68.97 ± 9.18  | 62.46 ± 12.31   |
| Female, N (%)                        | 17 (56.7)     | 16 (33.38)      |
| Hypertension, N (%)                  | 18 (60.0)     | 29 (90.4)       |
| Diabetes mellitus, N (%)             | 12 (40.0)     | 10 (30.8)       |
| Hyperlipidemia, N (%)                | 9 (30.0)      | 14 (40.2)       |
| Ischemic heart disease, N (%)        | 5 (16.7)      | 8 (22.2)        |
| Smoking, N (%)                       | 12 (40.0)     | 15 (42.9)       |
| Drinking, N (%)                      | 8 (26.7)      | 12 (35.0)       |
| Initial NIHSS, median (IQR)          | 6 (4–9)       | 5 (2–8)         |
| Onset to initial MRI, hours, mean (SD)| 10.77 ± 4.32 | 11.06 ± 3.77   |
| Length-of-hospital stay, days, mean (SD)| 9.73 ± 3.81 | 8.85 ± 3.90   |
| Lesion diameter, mm, mean (SD)       | 13.47 ± 4.46  | 11.48 ± 4.16   |
| ICAS, N (%)                          | 10 (33.3)     | 19 (55.6)       |
| ECAS, N (%)                          | 15 (50.0)     | 11 (32.3)       |
| WBC (×10⁹, x ± s)                    | 7.57 ± 2.92   | 6.83 ± 2.12     |
| RBC (×10¹², x ± s)                   | 4.54 ± 0.52   | 4.47 ± 0.62     |
| CRP (mg/l, x ± s)                    | 7.41 ± 3.48   | 6.69 ± 2.94     |
| Acute stain treatment, N (%)         | 13 (43.3)     | 26 (54.2)       |
| Dual-antiplatelet therapy, N (%)     | 10 (33.3)     | 14 (29.2)       |

### SBP parameter

| SBP | SSSI with PAD | SSSI without PAD |
|-----|---------------|------------------|
| SBPmean | 144.59 ± 7.65 | 141.04 ± 9.8    |
| SBPmax  | 189.30 ± 23.68 | 173.46 ± 17.49  |
| SBPmin  | 76.07 ± 26.31  | 61.08 ± 16.60   |
| SBP50   | 17.36 ± 4.94   | 14.43 ± 3.22    |
| SBPCV   | 12.27 ± 3.05   | 10.26 ± 2.35    |
| DBP | SSSI with PAD | SSSI without PAD |
| DBPmean | 82.58 ± 4.45  | 80.64 ± 4.59  |
| DBPmax  | 101.00 ± 8.39  | 94.10 ± 7.82 |
| DBPmin  | 36.50 ± 15.47  | 28.79 ± 9.31 |
| DBP50   | 8.00 ± 2.18    | 6.86 ± 2.05    |
| DBPCV   | 10.28 ± 2.66   | 8.56 ± 2.70    |

* p < 0.05.

** p < 0.1.
ischemic stroke during the study period, 501 patients initially met the

4.1. Demographic and general characteristics

Among 3352 consecutive patients who were diagnosed with acute ischemic stroke during the study period, 501 patients initially met the study eligibility criteria. Of them, 30 patients were excluded for early discharge and inadequate BP data. Twenty-five patients with history of stroke, 67 patients with cardiac embolic sources, 60 patients with significant stenosis in the responsible extracranial, and 23 patients treated with thrombolytic agents and interventional therapy were excluded. Finally, a total of 296 patients (mean age 64.60 ± 11.82 years, 110 female) were included in the analysis. The mean length from admission to initial MRI was 10.42 ± 4.31 h, and the mean hospital stay was 8.13 ± 3.13 days. The median NIHSS score was 4 (interquartile range, 3 to 7). Risk factors included hypertension in 174 (58.8%), diabetes mellitus in 64 (21.6%), hyperlipidemia in 72 (24.3%), current smoking in 8.13 ± 3.13 days. The median NIHSS score was 4 (interquartile range, 3 to 7). Risk factors included hypertension in 174 (58.8%), diabetes mellitus in 64 (21.6%), hyperlipidemia in 72 (24.3%), current smoking in 104 (35.1%), and drinking in 70 (23.6%). Thirty-five patients (11.8%) had histories of ischemic heart disease. PAD was found in 78 (26.4%), and concomitant ICAS was found in 70 (23.6%). ECAS in 55 (18.6%). Significant WMH was observed in 119 (40.2%) (Table 1).

4.2. Factors associated with END based on the status of parent artery

Of these, 30 (38.5%) patients with SSSIPAD and 53 (24.3%) patients without SSSIPAD developed END during the first 72 h after admission, respectively. For patients with SSSIPAD, age, sex, baseline NIHSS, lesion diameter, and ICAS were significantly associated with the development of END (P < 0.05). For those without, however, END was significantly related to age, sex, diabetes mellitus, baseline NIHSS, lesion diameter, ICAS, FBG and CRP (P < 0.05) (Table 1).

The relationships between BP parameters and END in patients with

Table 2

Comparison between patients with poor outcome and those with good outcome at 90 days after onset based on the status of parent artery.

| Characteristics                  | SSSI with PAD | SSSI without PAD |
|----------------------------------|---------------|------------------|
| Poor outcome (N = 16)            | Good outcome (N = 62) | Poor outcome (N = 38) | Good outcome (N = 180) |
| General clinical characteristics |               |                  |                   |
| Age, years, mean (SD)            | 69.81 ± 6.78  | 63.29 ± 10.97   | 67.92 ± 9.13      | 63.74 ± 12.33 |
| Female, N (%)                    | 8 (50.0)      | 25 (40.3)       | 20 (52.6)         | 57 (31.3)   |
| Hypertension, N (%)              | 10 (62.5)     | 37 (59.7)       | 25 (65.8)         | 102 (56.7) |
| Diabetes mellitus, N (%)         | 8 (50.0)      | 14 (22.6)       | 12 (31.6)         | 30 (16.7)   |
| Hyperlipidemia, N (%)            | 5 (31.2)      | 18 (29.0)       | 13 (34.2)         | 36 (20.0)   |
| Ischemic heart disease, N (%)    | 4 (25.0)      | 9 (14.5)        | 4 (10.5)          | 18 (10.0)   |
| Smoking, N (%)                   | 4 (25.0)      | 23 (37.1)       | 16 (42.1)         | 61 (33.9)   |
| Drinking, N (%)                  | 6 (37.5)      | 14 (22.6)       | 9 (23.1)          | 41 (22.8)   |
| Initial NIHSS, median (IQR)      | 8 (6–12)      | 6 (3–8)         | 7 (4–9)           | 4 (2–5)    |
| Onset to initial MRI, hours, mean (SD) | 10.75 ± 3.32  | 11.10 ± 3.85 | 10.37 ± 4.37      | 10.20 ± 4.44 |
| Length-of-hospital stay, days, mean (SD) | 9.50 ± 4.43  | 11.11 ± 3.74  | 7.95 ± 2.71       | 7.71 ± 2.75  |
| Lesion diameter, mm, mean (SD)   | 12.56 ± 4.83  | 12.17 ± 4.27   | 13.97 ± 3.09      | 10.88 ± 3.58 |
| LA (Fazekas scale ≥ 2), N (%)    | 8 (50.0)      | 21 (33.9)       | 12 (31.6)         | 78 (43.3)   |
| ICAS, N (%)                      | 5 (31.2)      | 14 (22.6)       | 5 (13.2)          | 31 (17.2)   |
| WBC (×10⁹/l, ± s)                | 7.05 ± 2.22   | 7.13 ± 2.54     | 7.93 ± 2.65       | 7.43 ± 2.19 |
| RBC (×10¹², ± s)                 | 4.70 ± 0.56   | 4.44 ± 0.58     | 4.39 ± 0.67       | 4.46 ± 0.57 |
| CRP (mg/l, ± s)                  | 7.25 ± 3.38   | 6.89 ± 3.13     | 7.99 ± 2.85       | 5.92 ± 2.37 |
| FBG (mmol/l, ± s)                | 19.62 ± 24.55 | 16.15 ± 15.22  | 18.75 ± 31.15     | 8.04 ± 11.56 |
| Current medications              |               |                  |                   |
| Acute stain treatment N (%)      | 7 (43.8)      | 32 (51.6)       | 17 (44.7)         | 102 (56.7) |
| Dual-antiplatelet therapy, N (%) | 7 (43.8)      | 17 (27.4)       | 10 (26.3)         | 54 (30.0)   |

BP values are presented as mean ± SD, median (interquartile range [IQR]), for continuous variables, or as the number (%) for categorical variables. Univariate parametric and nonparametric comparisons of clinical characteristics were performed with Student’s t-test, Mann–Whitney test, χ²-test or Fisher’s exact test as appropriate. Logistic regression analysis was developed using variables with P value ≤ 0.1 in univariate analysis to determine the independent association between BP variability and END. The SPSS package 16.0 was performed for all statistical analysis. Between-observer agreement with regard to artery status was analyzed with Cohen’s κ value. A two-tailed value of P < 0.05 was considered significant.

4.4. Factors associated with END based on the status of parent artery

Of these, 30 (38.5%) patients with SSSIPAD and 53 (24.3%) patients without SSSIPAD developed END during the first 72 h after admission, respectively. For patients with SSSIPAD, age, sex, baseline NIHSS, lesion diameter, and ICAS were significantly associated with the development of END (P < 0.05). For those without, however, END was significantly related to age, sex, diabetes mellitus, baseline NIHSS, lesion diameter, ICAS, FBG and CRP (P < 0.05) (Table 1).

The relationships between BP parameters and END in patients with
SSSIPAD and those without were analyzed respectively. In the SSSIPAD group, SBPmax, SBPmax-min, SBPsd, SBPcv, DBPmax, DBPmax-min, DBPsd, and DBPCV were significantly higher in patients with END than without END (P < 0.05). However, in the SSSI without PAD group, none of the BP parameters was found significantly associated with END. The ORs and 95% CIs for each BP parameter were calculated after adjusting for the following variables in multivariable models: age, sex, diabetes mellitus, baseline NIHSS, lesion diameter, Hyperlipidemia, CRP, and ICAS.

4.3. Factors associated with functional outcome

At 90 days after onset, 16 (20.51%) patient showed poor outcome in SSSIPAD and 38 (17.43%) patients in SSSI without PAD. Logistic regression analysis demonstrated that none of the BP parameters was found significantly associated with poor outcome in patients with SSSI (Tables 2 and 3).

5. Discussion

To date, there have been no clinical trials focusing on the heterogeneous aetiologies of SSSI. It was reported that SSSIPAD may more often show characteristics of atherosclerosis [23]. According to our study, the atherosclerosis indicators such as diabetes mellitus, hyperlipidemia, ICAS and ECAS were more prevalent in patients with SSSIPAD than those without, but the difference was not statistically significant. However, consistent with previous results that occlusion of the mouth of the branch due to atherosclerosis occurring in the parent artery was more prone to show worsening or fluctuating symptoms during hospitalization, we also found that SSSI associated with PAD more often suffered END [27,28]. Further prospective studies are required to elucidate the true impact of PAD on clinical prognosis of acute SSSI.

As we all know, END was a complication of stroke in general and subcortical stroke in particular. In this prospective study, the rate of END after acute SSSI in the whole population was 28.0%, similar to the END rates in previous studies that ranged from 12% to 43%, which can be explained by the diverse diagnostic criteria for END and the time interval to evaluation [4–11]. The objective of this study was to evaluate the effect of various BP parameters during the acute stage of ischemic stroke on END. Although there was some evidence to support the influence of BP on acute stroke outcome, conflicting results have been reported [15–19]. However, to the best of our knowledge, this was the first study to report an association between BP variability and the development of END in acute SSSI and further analyzed the association based on the parent artery status. A main finding of this study was that BP fluctuations during the acute stage, irrespective of the direction of the change, may have an important influence on END in patients with acute SSSIPAD, however not in those without. And therefore measures of BP variability may be better indicators of END in acute SSSIPAD.

Autonomic dysfunction in acute ischemic stroke has been extensively investigated. During the acute phase of ischemic stroke, the human brain has a decreased ability to auto regulate. BP is generally fluctuating during the acute stage, irrespective of the direction of the change, may have an important influence on END in acute SSSIPAD.
which lead to edema, hemorrhagic transformation, and infarct exten-
sion [17,18]. In addition, given that the orifice of the penetrating artery is
stenoed or occlusive because of presence of a plaque in the parent
artery, progression may be induced by reduced perfusion in the prox-
imal segment with increasing ischemia from the distal to the proximal
tissue area when suffered significant fluctuation in BP in patients with
SSSSIPAD [23,27,28]. It was reported that SSSI associated with PAD was
more located in the proximal region near the parent artery, where the
collateral vessels were absence, which might be another reason why
SSSSIPAD was more sensitive to fluctuating hemodynamics [23]. In
a word, we speculate that BP variability during this time period may
increase the risk of lesion growth, recurrence, and hemorrhagic trans-
formation or other vascular events, which might worsen early func-
tional outcome [29,30]. However, this information was not available in
the current study because of the absence of neuroimaging findings.

Several caveats must be made about this study. First, while the data
was prospective collected, the present study was a single-center study
and was limited by a small sample size. Our findings needed to be
further confirmed in multicenter prospective studies with large sam-
ple. Second, END following high BP variability might be attributed to
hemodynamic abnormalities, yet perfusion imaging or repeated MRI
was unavailable for us to directly assess this in this consecutive series of
patients, so the specific pathophysiology of END was not evidently
demonstrated. Forth, the effect of BP variability on the long-term
prognosis in patients with acute SSSI was not elucidated in this study,
and further prospective studies are required to answer this important
question.

In conclusion, our study demonstrated that the acute in-hospital BP
variability was associated with the development of END in patients with
acute SSSI. However, its impact varies depending on the status of parent
artery.

Disclosures

All the authors listed have approved the submitted manuscript and
we declare that we have no conflict of interest.

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