RESEARCH

In-depth hemodynamic assessment in acute mild stroke patients with large vessel occlusion or stenosis

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Abstract

Objective Acute treatment in mild stroke patients with acute anterior circulation large vessel occlusion/stenosis (AACLVO/S) had limited evidence. Hemodynamic play an important role in neurological deterioration. We aimed to investigate predictor value of hemodynamic assessment for clinical outcome predicting and guiding individual therapeutic decisions in those patients.

Methods We retrospectively analyze the stroke database in our stroke center. We recruited patients with mild stroke, defined by National Institutes of Health Stroke Scale (NIHSS) score ≤ 5, caused by AACLVO/S treated with just medical management (MT). They all received cerebral autoregulation (CA) assessments within 72 h after stroke onset. The primary end point was clinical outcome at 90-day after stroke.

Results Logistic regression analysis showed that bilateral higher baseline phase difference (PD) were independent variables related to favorable 90-day outcome, (OR 0.963, 95% CI 0.936–0.991, $p = 0.040$; OR 0.943, 95% CI 0.970–0.997; $p = 0.008$, respectively). The optimal cutoff value of bilateral PD was > 34.97º and > 14.29º respectively.

Conclusion CA evaluation can provide hemodynamic status in mild stroke patients with AACLVO/S.

Keywords Cerebral autoregulation, Mild stroke, Large artery stenosis, Outcome

Introduction

Around half of patients presented with mild ischemic stroke in clinical practice. It was reported that the risk of stroke of 12–20% within the first 3 months after mild stroke [1]. Therefore, several studies focus on the acute treatment in patients with mild stroke. Mild stroke is commonly identified using National Institutes of Health Stroke Scale (NIHSS) scores ≤ 3 or ≤ 5 [2]. Current clinical guidelines recommend endovascular treatment (EVT) as the standard of care for acute ischemic stroke (AIS) patients due to acute anterior circulation large vessel occlusion (AACLVO), such as the occlusion/stenosis of ICA and MCA with a baseline NIHSS score of ≥ 6 presenting within 6 h from symptom onset, or within 6–24 h from symptom onset [2]. However, there is finite evidence on the efficacy and safety of EVT in mild stroke patient cohort comparing with medical management [3, 4]. The mainly debate focused on potential benefits of EVT and complications including hemorrhage transformation, which are mostly correlated with hemodynamic dysfunction.

Cerebral autoregulation (CA) is an important reserve capacity to maintain an adequate hemodynamic

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stable despite changes in systemic blood pressure. It was reported impaired in acute stage of ischemic stroke [5].

The aim of this retrospective observational study is to identify the predictive value of CA in medical management decision for patients with acute mild ischemic stroke in the anterior circulation.

Methods

Study design and subjects

Data were obtained from the database, which is an ongoing acute stroke registry that prospectively sources records of patients with acute stroke admitted within seven days of onset. The study was approved by the Medical Ethics Committee of Nanfang hospital Southern Medical University, and written informed consents were obtained from all participants. All the patients received CA assessment from January 2018 to November 2021. Among those patients, who meet the following criteria were recruited. 1) > 18 years of age; 2) time from onset or last seen well of the symptoms to first CA assessment ≤ 72 h; 3) ischemic stroke was attributed to 70–99% stenosis of a major ipsilateral middle cerebral artery M1, proximal M2 segment, or intracranial internal carotid artery confirmed by Computed Tomography Angiography (CTA) and diffusion-weighted MRI; 4) Pre-enrollment Modified Rankin scale (mRS) score ≤ 2; 5) Sufficient bilateral temporal bone window for insonation of the MCA; 6) The modified Rankin Scale (mRS) up to 3 months after stroke were collected during a regular clinic visit or through a structured telephone interview conducted by an appropriately trained nurse.

Treatment protocol

All patients received MT according to relevant guidelines on admission. Clopidogrel genetic screening was performed to guide the modulation of antiplatelet treatment.

CA assessment

The baseline arterial blood pressure (ABP) was measured at the brachial artery using an automatic blood pressure monitor (Omron 711). Continuous blood flow velocity of MCA at a depth of 45 mm to 60 mm was obtained with 2 MHz probes which were attached to a customized head frame (EMS-9 PB, Shenzhen, China). The phase describes the phase shift from input to output at a specific frequency. The value of phase degree (PD) was unwrapped and limited to a range of $[-180^0, 180^0]$, and negative values were deleted. We adopted coherence to reflect the degree of the linear relationship between the complex values of input and output signals at different frequencies, and the value ranges from 0 to 1.

Clinical outcome

We collected clinical outcome: the score on the mRS at 3-months and recurrent stroke or TIA at 6 months after study enrollment by trained personnel who were blinded to the type of the treatment, by telephone and in the clinic. The mRS is a seven-point scale ranging from 0 (no symptoms) to 6 (death). A score of ≤ 2 indicates functional independence.

Statistical analysis

Kolmogorov–Smirnov analysis was used to test the normality of data distribution. Continuous variables were presented as mean ± standard deviation (SD), and non-normally distributed continuous variables were presented as median (interquartile range, IQR). Comparison between groups used Student's independent t-test or Mann-Whitney U test, depending on the normality of data. Student's paired t-test or Wilcoxon signed-rank test (non-parametric) was used for comparisons of paired samples. Categorical variables were presented as number and percentage, and compared with Pearson's χ [6] test or Fisher's exact test (if any expected value ≤ 5 was observed). Logistic regression models were used to investigate the association of independent variables to outcomes of patients. The receiver operation characteristics (ROC) curve was used to get the cutoff point of PD to predict the favorable outcome after MT. All statistical analyses were performed using IBM SPSS version 26 software (IBM Corporation, Somers, New York). In all analyses, a 2-tailed value of $P < 0.05$ was considered to indicate statistical significance.

Results

Demographics

Overall, 72 patients (mean age 59.50 ± 10.22 years; 69.44% males) fulfilled the inclusion criteria and were included in the study. Patients had a median NIHSS score of 1(0,5) on admission.

CA assessment in patients

Forty-six (63.89%) patients had favorable 90-day outcome. Univariate analysis showed significantly higher LDL, CRP, Fast blood glucose, NIHSS$_{on-admission}$, blood pressure$_{on-admission}$, infarct volume (Table 1), and significantly lower baseline bilateral PD in patients with unfavorable outcome than those with favorable outcome (50.86 ± 23.47˙vs. 29.81 ± 21.03˙, 36.16 ± 22.95˙vs. 18.40 ± 3.22˙), all $p < 0.05$. Logistic regression analysis was used to identify independent predictors of 90-day outcome. After adjusting confounding factors including LDL, CRP, Fast blood glucose, NIHSS$_{on-admission}$, blood pressure$_{on-admission}$, the bilateral higher baseline PD were independent variables related to favorable outcome. (adjustied OR 0.962, 95% CI 0.927–0.998; $p = 0.040$;

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Table 1 The baseline demographic and clinical characteristics of patients

	Total (n = 72)	Favorable outcome 46 (63.89%)	Unfavorable outcome 26 (36.11%)
Age, years	59.50 ± 10.22	58.76 ± 10.15	61.06 ± 10.28
Sex, *Male*	50 (69.44)	30 (65.22)	20 (76.92)
BMI, kg/m^2	24.58 ± 2.84	24.42 ± 2.80	24.79 ± 2.91
SBP, mmHg	142.82 ± 22.31	137.41 ± 22.55	150.15 ± 20.06[#]
DBP, mmHg	87.51 ± 13.93	85.28 ± 14.73	90.53 ± 12.36
Heart rate, bpm	70.62 ± 13.80	70.98 ± 12.63	70.09 ± 15.57
Smoking status			
Current smoker	36 (50.00)	22 (47.83)	14 (53.85)
Alcohol			
Current drinker	17 (23.61)	8 (17.39)	9 (34.62)
Hypertension	45 (62.50)	24 (52.17)	21 (80.77)
Diabetes mellitus	25 (34.72)	14 (30.43)	11 (42.31)
Hyperlipidemia	22 (30.56)	10 (21.74)	12 (46.15)
TG, mmol/L	1.76 ± 1.27	1.65 ± 1.11	1.92 ± 1.48
LDL, mmol/L	2.76 ± 0.89	2.55 ± 0.89	3.06 ± 0.82[#]
CRP, mg/L	5.60 ± 1.20	6.04 ± 0.97	12.77 ± 3.82[#]
Fast blood glucose, mmol/L	7.31 ± 5.79	5.80 ± 1.70	8.36 ± 1.43[#]
NIHSS on admission	1 (0, 5)	1 (0, 2)	2 (0, 5) [#]
Infarct volume (cm^3)	5.00 (2.30, 15.60)	3.30 (0.86, 7.91)	9.00 (5.00, 21.60) [#]
MTT contralateral	5.82 ± 1.16	5.57 ± 0.98	6.28 ± 1.40
MTT ipsilateral	7.69 ± 3.08	7.63 ± 2.77	7.81 ± 3.75
CBF contralateral	41.05 ± 8.75	40.29 ± 9.40	42.20 ± 7.83
CBF ipsilateral	33.10 ± 10.26	33.50 ± 10.65	32.53 ± 9.99
CBV contralateral	3.67 ± 0.76	3.66 ± 0.86	3.68 ± 0.59
CBV ipsilateral	3.76 ± 0.82	3.92 ± 0.76	3.47 ± 0.88
TTP contralateral	18.01 ± 4.57	17.59 ± 4.30	18.72 ± 5.15
TTP ipsilateral	19.48 ± 4.89	19.53 ± 5.27	19.40 ± 4.45

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; LDL, low-density lipoprotein; CRP, C-reactive protein; NIHSS, National Institute of Health stroke scale

BMI was calculated as weight in kilograms divided by height in meters squared

Data are presented as mean ± standard deviation, or number (percentage), or median (inter- quartile range, IQR)

[#] indicate significant difference comparing between outcome subgroups, $p < 0.05$

Table 2 Logistic regression analysis

|	Group with 90-day favorable outcome	Group with 90-day unfavorable outcome	adjusted OR	P
Baseline PD$_{contralateral\ hemisphere}$	50.86 ± 23.47°	29.81 ± 21.03°	0.962[#]	0.040[#]
Baseline PD$_{ipsilateral\ hemisphere}$	36.16 ± 22.95°	18.40 ± 3.22°	0.917[#]	0.008[#]

PD: phase degree

[#] indicates significant difference comparing between outcome subgroups, $p < 0.05$

adjusted OR 0.917, 95% CI 0.860–0.978; $p = 0.008$, respectively), Table 2. The ROC curve was performed to determine the cutoff point that optimized the sensitivity and specificity associated with 90-day clinical outcomes. The optimal cutoff value of the contralateral PD for predicting favorable outcome was >34.97° (sensitivity 75.80%, specificity 73.10%). The area under the curve of the ROC curve was 0.741, $p = 0.002$, (Fig. 1A). The optimal cutoff value of the ipsilateral PD for predicting favorable outcomes was >14.29° (sensitivity 90.90%, specificity 50.00%). The area under the curve of the ROC curve was 0.743, $p = 0.002$. (Fig. 1). We performed 90-day follow-up.

CA assessment showed that patients had lower CA value on the ipsilateral hemisphere with unfavorable outcome than those with favorable outcome 90-day after stroke, (39.36 ± 24.14° vs. 19.70 ± 17.16°, $p = 0.009$). Mean recurrence timepoint was 2.82 months. The detail clinical information was listed in Table 3.

Discussion

This study was the first to explore predictive value of CA in patients with mild stroke due to acute anterior circulation large vessel occlusion. The study showed that, in patients who received medical management, bilateral
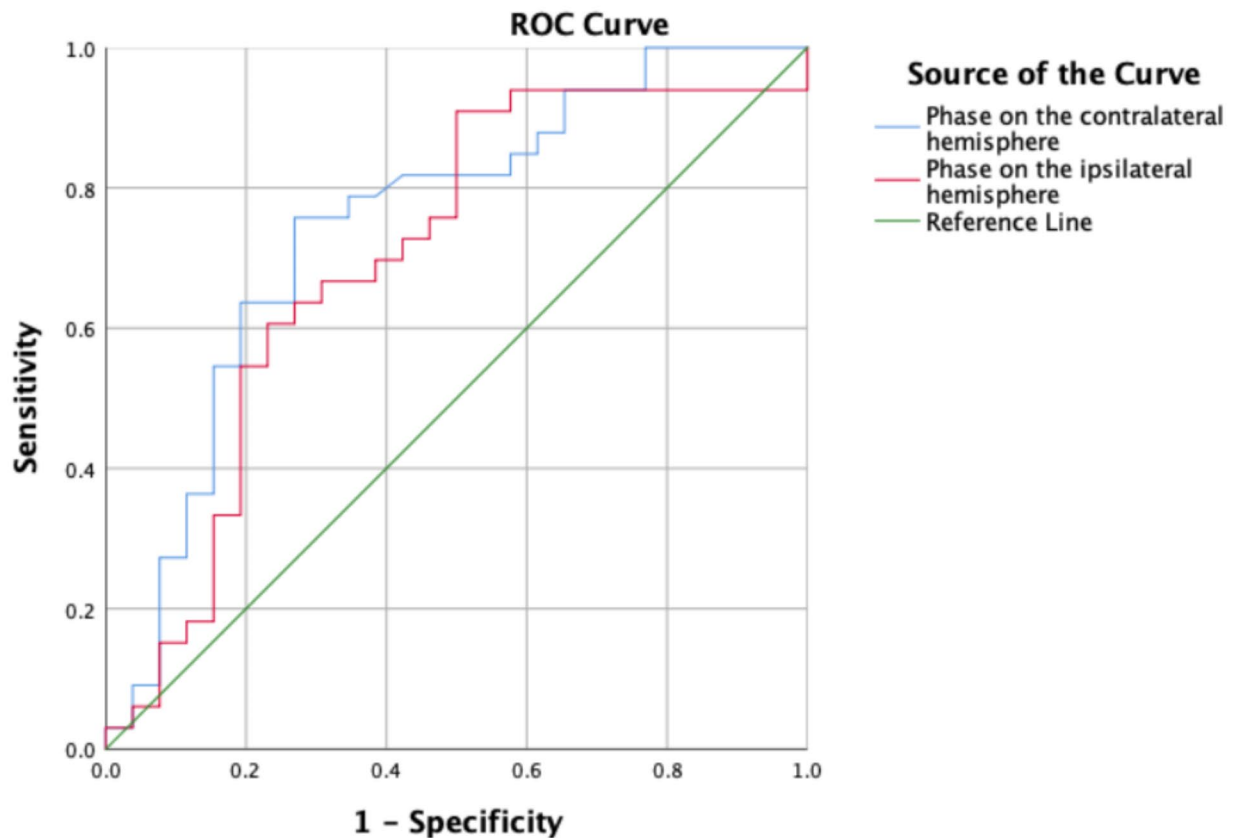
Fig. 1 The ROC curve showed the optimal cutoff value of the contralateral PD for predicting favorable outcomes was > 34.97° (sensitivity 75.80%, specificity 73.10%), the ipsilateral PD for predicting favorable outcomes was > 14.29° (sensitivity 90.90%, specificity 50.00%) in MT-group$_{within90-day}$

Table 3 Comparison of phase degree between different groups

	Patients with 90-day favorable outcome	Patients with 90-day unfavorable outcome	*P*
PD$_{contralateral\ hemisphere}$	50.86 ± 23.47	29.81 ± 21.03	0.040
PD$_{ipsilateral\ hemisphere}$	36.16 ± 22.95	18.40 ± 3.22	0.008
PD$_{contralateral\ hemisphere}$ 90-day after stroke	53.43 ± 21.04	30.45 ± 18.68	0.253
PD$_{ipsilateral\ hemisphere}$ 90-day after stroke	39.36 ± 24.14°	19.70 ± 17.16°	0.009

P: *p*-value of PD between different outcome subgroups after adjusting confounding factors

PD: phase degree

higher baseline PD were independent variables related to favorable 90-day outcome. And the optimal cutoff value of the contralateral and ipsilateral PD for predicting favorable outcome was > 34.97°, > 14.29° respectively.

Several studies indicated that the hemodynamics of the stenosis is extremely complicated, and the anatomical stenosis should not be considered only, but should be combined with CA ability and collateral circulation compensation. Therefore, we assessed CA in the study. CA was a hemodynamic parameter which is the intrinsic ability of the cerebral vasculature to guarantee downstream blood supply and reflects cerebrovascular reserve

capacity. Previous researches reported that CA impairments globally in ischemic stroke patients, affecting both the ipsilateral and the contralateral hemispheres [5, 7]. We got the similar finding, and we found that bilateral higher baseline CA were independently associated with favorable 90-day outcome in MT group. It means that in patients with mild stroke caused by AACLVO, if they had bilateral value of PD higher than the reference values mentioned above, MT was suggested to be selected. A possible explanation is that CA played an important role in protecting hemodynamic fluctuation under hypoperfusion condition, which is considered as the major cause

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of ischemic stroke. Under ischemic condition, not only the affected side CA, but also the unaffected side play the compensatory role.

Meanwhile, failure of CA is reported to be associated with secondary brain injury that may occur as an extension of the initial ischemic core, "no-reflow phenomenon", cerebral edema, or hemorrhagic transformation [8]. All these secondary complications above play important role in outcome after acute ischemic stroke. As we know, not all patients would benefit from mechanical thrombectomy (MT).

CA monitoring utilizing TCD needed 20 min, which should be done in the acute phase before making medical management [9]. However, we believe that treatment should be individualized and that it is worthwhile to spend 20 min for a full hemodynamic assessment before making a medical decision. Intact CA during AIS has not only been shown to be responsible for a smaller infarct volume but also protects the vulnerable penumbra [10]. Further convenient CA assessment methods are needed.

The current study has several limitations. First, we recruited more male subjects than female in our study, since there are more male stroke patients than female in China, and female subjects are more likely to have insufficient bilateral temporal bone windows for insonation due to the low density of the temporal bone. Secondly, the relatively small number of patients, which affected the statistical analysis of the various groups. And we just performed 90-day and 6-month follow-up, but not long-term follow-up. Further relative data is needed. Thirdly, our result is limited by its design and lack of the control arm. However, currently, there are no prospective, randomized trials that compare endovascular management with aggressive medical therapy. Further randomized trials using the cut-off value is needed. Fourthly, more detail factors were not further analyzed. For those patient population, there are still numerous researches be performed. Lastly, we did not analyze the correlations between the size of cerebral infarctions and CA, we will perform relative analysis in future.

In conclusion, CA evaluation can provide the assessment of hemodynamic status in patients with symptomatic subacute/chronic MCA stenosis. Then help determine which patients will benefit from MT and prognostic information.

Data availability
The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

Declarations

Ethics approval and consent to participate
The study was approved by the Medical Ethics Committee of Nanfang Hospital. Written informed consent was obtained from all participants. The data presented were collected for the purpose of quality assurance and, thus, the identity of the individual patients was anonymous.

Consent for publication
Not applicable.

Clinical trial number
Not applicable.

Medical ethics registration number
NFEC-201,910-K4.

Competing interests
The authors declare no competing interests.

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