Dynamic Cerebral Autoregulation Is an Independent Functional Outcome Predictor of Mild Acute Ischemic Stroke

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Background and Purpose—Cerebral autoregulation is impaired in patients with acute ischemic stroke. The purpose of this study was to investigate whether dynamic cerebral autoregulation (dCA) indices constitute an independent functional outcome predictor of acute ischemic stroke.

Methods—In this study, 86 patients at days 3 to 7 after acute ischemic stroke and 40 age- and sex-matched controls were enrolled for assessing their dCA indices under spontaneous hemodynamic fluctuations. The dCA indices of patients with favorable outcomes (modified Rankin Scale score ≤1 at 3 months, n=65), patients with unfavorable outcomes (modified Rankin Scale score ≥2 at 3 months, n=21), and controls were compared.

Results—The dCA indices, namely the phase shift at very low frequency band (phase_VLF), in the patients with unfavorable outcomes were significantly worse than those in the patients with favorable outcomes. However, the phase_VLF in the patients with favorable outcomes did not differ from those in the controls. Impaired dCA was associated with elevated mean arterial pressure and large infarction volume but was also present in patients with normal mean arterial pressure or small infarction volume. Phase_VLF was a predictor of outcomes in the receiver operating characteristic analysis (area under the curve: 0.722; $P<0.001$). Multivariate analysis revealed that a phase_VLF value of <61° was independently associated with unfavorable outcomes (odds ratio=4.90; $P=0.024$).

Conclusions—Phase_VLF is an independent functional outcome predictor of acute ischemic stroke. (***Stroke*****. 2018;49:2605-2611. DOI: 10.1161/STROKEAHA.118.022481.)**

Key Words: arterial pressure ■ autoregulation ■ blood pressure ■ infarction ■ odds ratio ■ stroke

Cerebral autoregulation (CA) is the mechanism ensuring the maintenance of constant cerebral blood flow (CBF) over a specific range of systemic hemodynamic changes.[1] Impaired CA has been observed in patients with traumatic brain injury,[2–4] ischemic and hemorrhagic strokes,[5–7] and cerebral vascular stenosis.[8–10] When blood pressure (BP) increases or decreases beyond the range of CA control, CBF becomes unstable and secondary injury occurs. In acute ischemic stroke (AIS), CA regulates vascular tone to compensate hypoperfusion during ischemia and attenuates hyperperfusion after vascular recanalization. Although severe hypertension or hypotension has consistently been associated with unfavorable outcomes in AIS in many studies, no scientifically determined standard control target for BP is available.[11] CA is a potential reference for BP control in the care of patients with stroke but is not assessed in clinical practice yet. In studies on AIS, impaired CA has been found in bilateral hemispheres,[7,12–14] and it is dominant on the affected side in patients with large infarction.[7,13,15,16] The severity of CA impairment is associated with the infarction volume.[13,17] However, whether CA impairment is independently associated with the outcome or simply the consequences of other known conditions affecting the outcome of AIS, such as abnormal BP or large infarction volume, remains unclear. In a previous systemic review, the association between CA and the outcomes of AIS could not be determined because of the lack of relevant studies.[18]

Dynamic CA (dCA) is an approach to quantify CA, and it assesses CA by analyzing the relationship between transient changes in CBF and BP.[19] CBF and BP are measured using a Doppler ultrasonography monitor and a noninvasive BP monitor, respectively.[1,20,21] Several well-documented dCA indices can be obtained in the resting state,[22–24] which facilitate dCA assessment in clinical practice. Our objective was to test the validity of resting-state dCA as a functional outcome predictor of AIS and analyze its association with other clinical characteristics to determine whether resting-state dCA is an independent functional outcome predictor.

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Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Participants

This study was approved by the Institutional Review Board of Taipei Medical University. Patients with AIS, confirmed through magnetic resonance imaging, and a premorbid modified Rankin Scale (mRS) score of 0 were consecutively screened when they were admitted to Taipei Medical University Shuang Ho Hospital within 7 days after stroke onset. We did not limit the ischemic vascular territory as an inclusion criterion. Patients with (1) atrial fibrillation, (2) total occlusion of the internal carotid artery, and (3) pure sensory impairment at admission were excluded from the study. Moreover, dCA in the patients who participated in the study was assessed between days 3 and 7 after stroke onset, and stroke severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS) on the day of dCA assessment. For this study, 100 patients were recruited, and 40 age- and sex-matched volunteers without a history of cerebrovascular disease were recruited as controls. Written informed consent was obtained from each participant. Patients with mRS scores of ≤1 at 3 months were defined as having favorable outcomes, whereas those with mRS scores of ≥2 at 3 months were defined as having unfavorable outcomes.

CA Measurement and Analysis

In this study, we measured dCA under spontaneous fluctuations in BP and CBF velocity (CBFV) of 5 minutes by using the methods as our previous studies.[25,26] In brief, CBFV of extracranial internal carotid artery was recorded by using a Doppler ultrasonography monitor, and BP was recorded by using a noninvasive BP monitor based on finger plethysmography. The mean arterial pressure (MAP) and mean CBFV were obtained by averaging the BP and CBFV waveform, respectively. One common dCA algorithm, namely transfer function analysis (TFA) recommended by the International Cerebral Autoregulation Research Network (CARNet, http://www.car-net.org/content/resources), was applied in this study.[27] TFA was used to calculate the phase shift, gain, and coherence between BP and CBFV in frequency bands in which dCA is active, namely very low frequency (VLF, 0.02–0.07 Hz) and low frequency (LF, 0.07–0.20 Hz). The changes in CBFV are smaller and are restored faster than those in BP, which could be quantified as the gain and phase shift between BP and CBFV waveforms. In patients with impaired CA, TFA reveals a larger gain and a smaller phase shift between the BP and CBFV waveforms than those observed in patients with intact CA.[1,24] In this study, 14 patients whose ipsilesional phase shifts at VLF (phase_VLF) could not be calculated owing to an unacceptably low coherence (<0.34) between BP and CBFV were excluded because the TFA results in these patients were unreliable.[28] Eighty-six patients' data were included in the final analysis. The methods in detail are described in the online-only Data Supplement.

Neuroimaging Analysis

Brain magnetic resonance imaging, including T1- and T2-weighted imaging, T2 fluid-attenuated inversion recovery imaging, diffusion-weighted imaging (DWI), and time-of-flight magnetic resonance angiograms, was the routine examination for all the patients with AIS, but it was not performed for the controls. In each patient, the lesion volume and location in the DWI were interpreted manually, and preexisting white matter hyperintensities in the T2 fluid-attenuated inversion recovery images were estimated using the Fazeka scale.[29]

Statistical Analysis

Data normality was determined using the Shapiro-Wilk test. Normally distributed data are expressed as means±SDs, whereas non-normally distributed data are expressed as medians with interquartile ranges. Most dCA indices were non-normally distributed. The demographic data and dCA indices in the patients with favorable outcomes, patients with unfavorable outcomes, and controls were compared using ANOVA, the Kruskal-Wallis test, or the χ^2 test and post hoc analysis, as applicable. The dCA indices were compared between bilateral sides by using the Wilcoxon signed-rank test. The average value of the bilateral sides of each dCA index in the controls was compared with either the ipsilesional or contralesional side of each dCA index in the patients. Moreover, dCA indices that were significantly different between the patients with favorable outcomes and those with unfavorable outcomes were selected for further analysis. Receiver operating characteristic analysis was used to test the sensitivity and specificity, as well as to determine the best cutoff value, of the indices in identifying patients with unfavorable outcomes. A univariate logistic regression analysis was conducted to estimate the odds ratios of unfavorable outcomes for the demographic variables and ipsilesional dCA indices. The variables associated with unfavorable outcomes in the univariate logistic regression analysis were included in a multivariate logistic regression model to adjust the odds ratios of unfavorable outcomes. The correlation between dCA indices and other variables was examined using the Spearman rank correlation coefficient. $P<0.05$ was considered statistically significant. Statistical data were analyzed using MedCalc Statistical Software (version 18, MedCalc Software bvba, Ostend, Belgium).

Results

The clinical characteristics of the controls (n=40), patients with favorable outcomes (n=65), and patients with unfavorable outcomes (n=21) are summarized in Table 1. The age and sex among the 3 groups did not differ significantly. The prevalence of hypertension, diabetes mellitus, and hyperlipidemia was significantly higher in the patients with favorable outcomes or in those with unfavorable outcomes than in the controls; however, the prevalence did not differ significantly between the patients with favorable outcomes and those with unfavorable outcomes. The MAP in the patients with unfavorable outcomes was significantly higher than that in the controls, but the MAP did not differ significantly between the patients with favorable outcomes and those with unfavorable outcomes. The mean CBFV on bilateral sides was not different between controls, patients with favorable outcomes, and patients with unfavorable outcomes. Among the 86 patients with AIS, 61 (71%) had lesions in the corticospinal tract as revealed by DWI. Furthermore, the stroke pathogeneses in 55 (64%) and 31 (36%) patients were small vessel disease and large artery atherosclerosis, respectively. The distribution of acute ischemic lesion location of the patients was listed in the Table I in the online-only Data Supplement. Most of the patients exhibited mild stroke severity (NIHSS: median=3; interquartile range: 2–5; range: 1–22), small lesion volume in DWI (median=0.7 cm^3; interquartile range: 0.4–1.9 cm^3; range: 0.1–84.1 cm^3), and mild preexisting white matter hyperintensities (median scores on the Fazekas scale=0 and 1 for periventricular white matter and deep white matter, respectively); however, 21 patients (24%) exhibited unfavorable outcomes (mRS score ≥2 at 3 months).

The dCA indices, namely phase_VLF, phase shift at LF, normalized gain (%/%) at VLF (gain_VLF), and normalized gain at LF in the controls, patients with favorable outcomes, and patients with unfavorable outcomes are presented in Figure 1. The phase_VLF value in the patients with unfavorable outcomes was significantly lower than those in the patients with favorable outcomes and controls on both

Table 1. Clinical Characteristics of the Participants (n=126)

	Controls (n=40))	Patients With Favorable Outcomes (n= 65)	Patients With Unfavorable Outcomes (n=21)	*P* Value
Age, median (IQR)	59 (55–64)	57 (50–64)	59 (54–63)	0.516
Male sex	31 (78%)	48 (74%)	18 (86%)	0.530
Hypertension	15 (38%)	50 (77%)*	19 (91%)*	<0.001†
MAP (mean±SD)	81±15 mm Hg	89±19 mm Hg	98±23 mm Hg*	0.003†
Diabetes mellitus	6 (15%)	23(35%)*	11 (52%)*	0.008†
Hyperlipdemia	16 (40%)	46 (71%)*	16 (76%)*	0.002
Lesion on the left side		39 (60%)	12 (57%)	1.000
NIHSS at acute stage, median (IQR)		3 (2–4)	5 (3–7)‡	0.004†
mRS at 3 mo, median (IQR)		1 (1–1)	2 (2–3)‡	<0.001†
Stroke pathogenesis				0.602
Large artery atherosclerosis		22 (34%)	9 (43%)	
Small vessel disease		43 (66%)	12 (57%)	
DWI lesion volume, median (IQR)		0.7 (0.3–1.3) cm^3	1.5 (0.5–4.7) cm^3	0.079
DWI lesion at corticospinal tract		43 (66%)	18 (86%)	0.104
White matter hyperintensities in T2 FLAIR				
Periventricular Fazekas scale, median (IQR)		0 (0–1)	1 (0–1)	0.417
Deep white matter Fazekas scale, median (IQR)		1 (0–1)	1 (0–1)	0.707
Mean CBFV				
Ipsileisonal, median (IQR)	35 (27–39) cm/s	32 (25–37) cm/s	30 (22–36) cm/s	0.097
Contralesional, median (IQR)	35 (27–39) cm/s	32 (24–40) cm/s	30 (27–38) cm/s	0.473

The mean cerebral blood flow velocity in controls is the average value of bilateral sides. CBFV indicates cerebral blood flow velocity; DWI, diffusion-weighted image; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; MAP, mean arterial pressure; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Different from controls.

†$P<0.05$.

‡Different from patients with favorable outcomes.

sides (ipsileisonal phase_VLF: 47°, 63°, and 57°, respectively, $P=0.006$; contralesional phase_VLF: 45°, 62°, and 57°, respectively, $P=0.011$). However, the phase shift at LF, gain_VLF, and normalized gain at LF values did not differ significantly among the 3 groups on both sides although gain_VLF on both sides and normalized gain at LF on ipsilesional side in the patients with unfavorable outcomes showed a trend higher than those in the patients with favorable outcomes and controls (ipsileisonal gain_VLF: 1.19, 1.03, and 1.04, respectively, $P=0.233$; contralesional gain_VLF: 1.19, 1.09, and 1.05, respectively, $P=0.212$; ipsilesional normalized gain at LF: 1.37, 1.21, and 1.32, respectively, $P=0.442$). In the patients with favorable outcomes, all the dCA indices on both sides did not differ significantly from those in the controls on both sides. Furthermore, all the dCA indices did not differ significantly between both sides in the patients and controls.

In patients with AIS (n=86), a small negative association was observed between the ipsilesional phase_VLF and MAP (correlation coefficient=–0.284; $P=0.008$; Figure 2A). The ipsilesional phase_VLF was not significantly associated with DWI lesion volume (correlation coefficient=–0.022; $P=0.841$; Figure 2B) or the Fazeka score (correlation coefficient=–0.069; $P=0.525$). Nevertheless, the ipsilesional phase_VLF in the patients with DWI lesion volume ≥5 cm^3 (n=8) were significantly worse than those in patients with DWI lesion volume <5 cm^3 (n=78; 37° versus 61°; $P=0.015$). Although impaired dCA (small phase_VLF) was associated with elevated MAP and large lesion volume, it was also present in patients with normal MAP (Figure 2A) or small lesion volume (Figure 2B).

In the receiver operating characteristic analysis, the area under the curve of the ipsilesional and contralesional phase_VLF of the patients with unfavorable outcomes was 0.722 (95% CI=0.615–0.813; $P<0.001$) and 0.718 (95% CI=0.604–0.815; $P<0.001$), respectively. The optimal cutoff value of phase_VLF for predicting unfavorable outcomes was <61° for ipsilesional phase_VLF (sensitivity 81%, specificity 58%) and <58° for contralesional phase_VLF (sensitivity 84%, specificity 57%). The area under the curve of phase_VLF did not differ significantly between bilateral sides ($P=0.932$). The area under the curve of the MAP was 0.619 (95% CI=0.508–0.722; $P=0.105$), which did not differ significantly from a

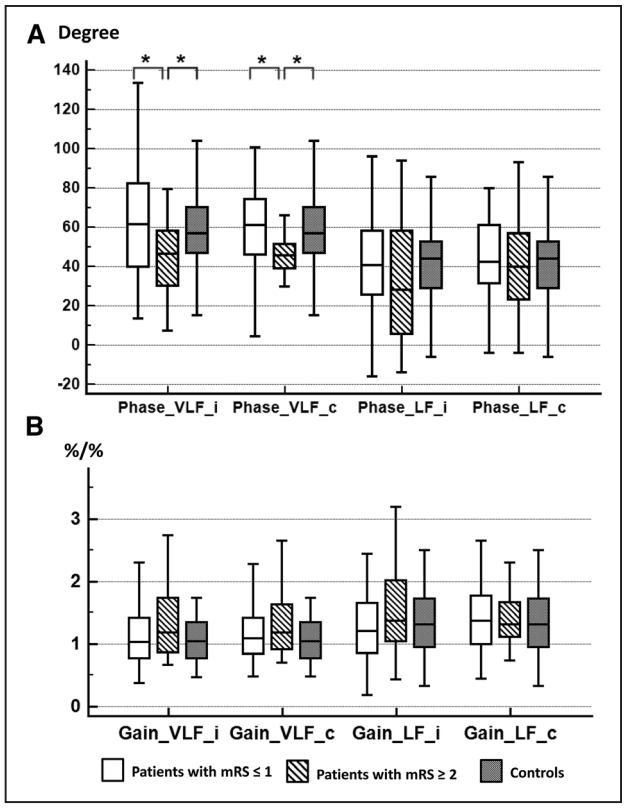

Figure 1. Comparison of autoregulation indices between groups. Box-and-whisker plots of (**A**) phase shift at very low frequency (phase_VLF) and phase shift at low frequency (phase_LF), and (**B**) normalized gain (%/%) at very low frequency (gain_VLF), and normalized gain at LF (gain_LF) between patients with favorable outcomes (modified Rankin Scale [mRS] score ≤1), patients with unfavorable outcomes (mRS score ≥2), and controls. *Significantly different in the post hoc analysis of Kruskal-Wallis test. c indicates contralesional side; and i, ipsilesional side.

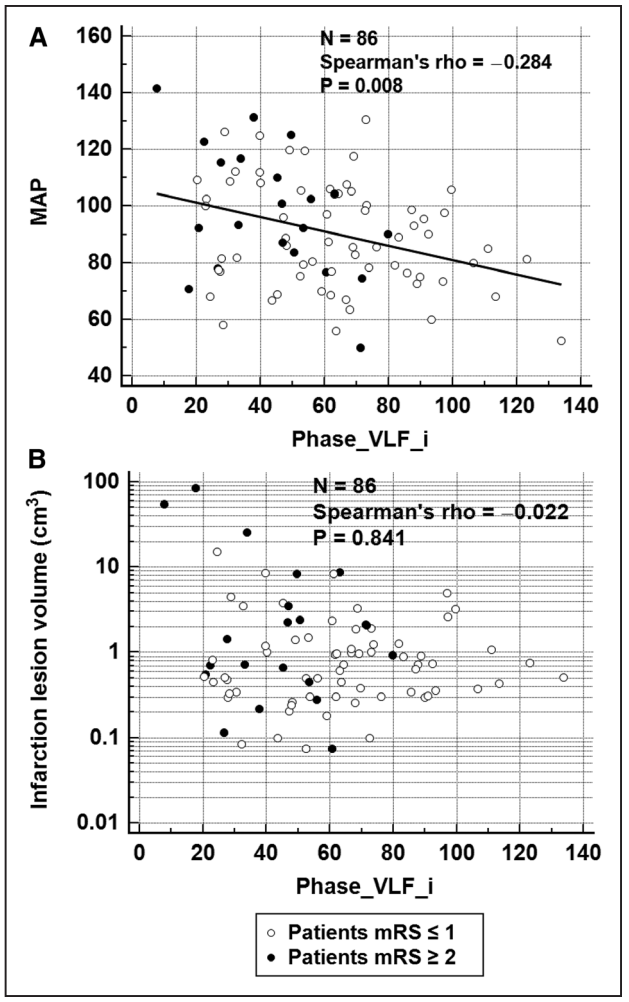

Figure 2. Association between autoregulation indices and clinical characteristics. Scatter plots of (**A**) phase shift at very low frequency (phase_VLF)–mean arterial pressure (MAP) with regression line, (**B**) phase_VLF–infarction lesion volume. The regression line is not drawn in (**B**) because of no significant association exists between variables. i indicates ipsilesional side; and mRS, modified Rankin Scale.

random guess. Therefore, phase_VLF is a valid predictor of unfavorable outcomes in AIS.

The results of univariate and multivariate logistic regression analyses of variables predicting unfavorable outcomes are presented in Table 2. In the univariate analysis, the NIHSS score and an ipsilesional phase_VLF value of <61° were significant predictors, whereas MAP, DWI lesions in the corticospinal tract, and DWI lesion volume were borderline significant predictors (P=0.080, 0.097, and 0.087, respectively). To obtain a reliable multivariate logistic regression model, a minimum of 5 outcome events per predictor variable are required.[30] Given the 21 events of unfavorable outcomes in this study, the multivariate logistic regression model allows up to 4 independent predictor variables. We choose 3 variables other than phase_VLF which had the lowest P values in the univariate analysis, namely MAP, NIHSS at acute stage, and DWI lesion volume, to be included in the multivariate models. In the multivariate analysis, MAP and DWI lesion volume remained nonsignificant, and the NIHSS score and ipsilesional phase_VLF value of <61° remained significant. Therefore, an ipsilesional phase_VLF value of <61° is an independent outcome predictor in patients with AIS. Patients with AIS with an ipsilesional phase_VLF value of <61° have a 4.90-fold higher risk of exhibiting an unfavorable outcome than those with an ipsilesional phase_VLF value of ≥61° do.

Discussion

By using a sample size of 86 patients, we explored the association between dCA indices and clinical characteristics and determined an optimal cutoff value of the dCA index for outcome prediction, which are usually necessary in clinical practice and can facilitate future studies. Impaired dCA was found in patients with severe hypertension and large infarction volume.[13,17,31] In this study, a certain portion of patients with normal MAP and small lesion volume still had impaired dCA. In addition, dCA indices were impaired in not only the ipsilesional but also the contralesional side. Therefore, dCA is influenced by multiple factors, and a substantial portion of impaired dCA is likely caused by mechanisms other than AIS or abnormal BP. Intervention in dCA is possible by controlling BP or using angiotension II receptor blocker.[32–34] Therefore, impaired dCA is a potential therapeutic target rather than a consequence of ischemic injury.

In this study, phase_VLF but not gain_VLF was significantly associated with outcome. In hemorrhagic stroke, gain was found markedly increased but not consistently associated with outcome.[5,35] In ischemic stroke, gain is less prominently

Table 2. Multivariate Logistic Regression Analysis of Clinical Characteristics and dCA Indices

Characteristics (n=86)	Unfavorable Outcome (mRS ≥2 at 3 mo)			
	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age	1.02 (0.97–1.08)	0.339		
Male sex	2.13 (0.56–8.13)	0.271		
Hypertension	2.85 (0.59–13.7)	0.190		
MAP	1.02 (1.00–1.05)	0.080	1.01 (0.97–1.04)	0.730
Diabetes mellitus	2.01 (0.74–5.44)	0.170		
Hyperlipidemia	1.32 (0.42–4.12)	0.631		
NIHSS at acute stage	1.42 (1.11–1.80)	0.004*	1.54 (1.15–2.05)	0.003*
DWI lesion on the left side	0.89 (0.33–2.41)	0.817		
DWI lesion at corticospinal tract	3.07 (0.82–11.56)	0.097		
DWI lesion volume	1.13 (0.98–1.29)	0.087	1.13 (0.98–1.30)	0.085
Periventricular Fazekas scale	1.30 (0.70–2.40)	0.408		
White matter Fazekas scale	1.06 (0.52–2.13)	0.880		
Ipsilesional mean CBFV	0.98 (0.93–1.03)	0.346		
Contralesional mean CBFV	0.98 (0.94–1.03)	0.526		
Ipsilesional phase shift VLF <61°	5.98 (1.81–19.77)	0.003*	4.90 (1.24–19.40)	0.024*

CBFV indicates cerebral blood flow velocity; dCA, dynamic cerebral autoregulation; DWI, diffusion-weighted imaging; MAP, mean arterial pressure; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and VLF, very low frequency.

*$P<0.05$.

increased,[12,17] which is consistent with the result of this study. However, in both hemorrhagic and ischemic strokes, phase shift was consistently reported decreased and associated with outcome.[5,17] It is possible that the speed of CBF change (phase shift) is more sensitive in detecting dCA impairment than the amplitude of CBF change (gain).

In the studies of dCA and AIS by Reinhard et al[13] and Castro el al,[17] phase shifts (0.06–0.12 and 0.03–0.15 Hz, respectively) were associated with mRS score >2 at 3 months in patients with moderate to severe stroke (median baseline NIHSS score=9 in both studies). In the multivariate analysis, the association between phase shift and outcome disappeared in the study by Reinhard et al[13] but was still present in the study by Castrol et al.[17] In our study, most patients were with mild disease severity (median baseline NIHSS score=3), and phase_VLF remained an unfavorable outcome predictor in the multivariate analysis. Therefore, phase shift is an effective outcome predictor in both severe and mild AIS. But the study by Castro et al[17] suggested a cutoff phase shift <37° to predict unfavorable outcomes, whereas our study suggested a cutoff phase shift <61°. This difference may be because of the different frequency band selection in TFA, different disease baseline severity, and different outcome definition. A unified TFA algorithm may help to make future studies comparable to each other. It is worth noting that the study by Reinhard et al[13] and our study both showed no significant difference in the dCA indices between the patients with AIS and the controls, signifying that some patients exhibited adequate dCA despite stroke and some of the controls exhibited impaired dCA without stroke. Therefore, dCA in AIS is not only a consequence of brain infarction but also affected by systemic conditions. It has been known that dCA is impaired in patients with hypertension and diabetes mellitus,[31,36,37] and it could be the reason of some controls exhibiting impaired dCA.

Uncontrolled hypertension or hypotension is a known risk factor for unfavorable outcomes of stroke, and a U-shaped relationship between baseline BP and outcome has been consistently reported in many observational studies.[38–41] The proposed mechanism is that extreme fluctuations in BP, which are beyond the limit of CA, result in inadequate CBF and secondary injury.[42,43] However, CA is not currently used in clinical practice because various methods of CA measurement have been proposed, and no gold standard is recommended yet. In this study, we used the dCA protocol under spontaneous BP and CBF fluctuations in the resting state, which are feasible for clinical practice because they do not require patients' cooperation or BP manipulation. Under the current dCA protocol, it showed that phase_VLF is associated with MAP, signifying that high BP is associated with impaired CA. Although we did not find an optimal MAP cutoff value for predicting outcomes in the receiver operating characteristic analysis, a phase_VLF value of <61° remained an outcome predictor after adjustment for all possible confounders. It has been found that both upper and lower MAP thresholds of CA shift upward in chronic hypertension,[44] and it may explain why it is not possible to find a standard control target of BP in patients with AIS. Therefore, phase_VLF may be a more sensitive hemodynamic biomarker than BP in the care of patients with AIS.

This study has limitations. First, the average NIHSS score, lesion volume, and Fazekas score of the patients indicated mild ischemia. Second, patients with atrial fibrillation, who account for a considerable portion of patients with

AIS, were not included in this study because the feasibility of the dCA model in patients with atrial fibrillation has yet to be established. Third, we did not conduct validation tests of the cutoff values of phase_VLF in this study; conducting such tests requires a new group of patients. Fourth, 14 of 100 patients were excluded from the final analysis because of the unacceptably low coherence of the VLF in the TFA algorithm, and a dCA recording time >5 minutes may reduce the incidence of this problem. Fifth, the MAP in this study was calculated from the BP monitor based on finger plethysmography but not arm sphygmomanometer; there is known systematic error of BP measurement when using finger plethysmography.

In conclusion, the dCA indices, namely phase_VLF, is worse in bilateral hemispheres in patients with unfavorable outcomes than in those with favorable outcomes in AIS. Phase_VLF is independently associated with functional outcomes. Impaired dCA can be present in patients with normal BP or small infarction volume. Future studies are required to validate our findings and investigate the treatment effect of intervening in dCA indices in patients with AIS.

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Disclosures

None.

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