Dynamic Cerebral Autoregulation in Acute Ischemic Stroke Assessed From Spontaneous Blood Pressure Fluctuations

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Background and Purpose—This study investigates dynamic cerebral autoregulation assessed from spontaneous blood pressure (ABP) and cerebral blood flow velocity (CBFV) fluctuations and its time course in acute ischemic stroke.

Methods—Forty patients admitted with acute ischemic stroke in the territory of the middle cerebral artery (MCA) were enrolled. Admission National Institutes of Health Stroke score was 6±4. Study 1 was performed within 22 (±11) hours and study 2 was performed within 134 (±25) hours of ictus. The final analysis comprised 33 and 29 patients for study 1 and study 2, respectively. Twenty-five age- and sex-matched controls were studied. ABP (Finapres method) and CBFV in both MCAs (transcranial Doppler) were recorded over 10 minutes. Correlations between diastolic and mean ABP and CBFV fluctuations were averaged, yielding the correlation coefficient indices (Dx, Mx). Transfer function analysis was applied to obtain phase shift and gain between ABP and CBFV oscillations.

Results—No disturbance of autoregulation was indicated by all parameters at study 1. Separate analyses for clinical severity, stroke side, and size did not reveal significant differences for the various autoregulatory indices at study 1 and 2. At study 2, MCA flow velocity was significantly increased on both sides, the autoregulation index Mx was slightly but significantly ($P<0.05$) worse on both sides in comparison to study 1, and phase showed a trend toward poorer values on affected sides. No significant differences to controls occurred. Clinical outcome in patients completing both studies was good in all but one patient.

Conclusions—Dynamic cerebral autoregulation assessed from spontaneous blood pressure fluctuations does not seem to be relevantly disturbed in early minor MCA stroke. At the subacute stage, slight autoregulatory disturbance may be present. (***Stroke***. 2005;36:1684-1689.)

Key Words: cerebral ischemia ■ stroke ■ ultrasonography, Doppler, transcranial

The presence or absence of cerebral autoregulation in acute stroke is critical for maintenance of stable blood flow in the ischemic penumbra and for avoidance of excessive hyperperfusion. Most of the early experimental and clinical studies on autoregulation in acute stroke have used different arterial blood pressure (ABP) steady-states ("static autoregulation"). Focal impairment of static autoregulation in the reperfused ischemic area itself has been demonstrated.[1] Cerebral autoregulation also seems to be deranged in collateral vessels supplying the ischemic penumbra during vessel occlusion.[2] Moreover, some studies indicated a more global impairment of static autoregulation in the affected and also in the unaffected hemisphere,[3] whereas a recent study found static autoregulation in the unaffected hemisphere to be generally preserved.[4]

Because assessment of static autoregulation requires considerable manipulation of ABP, it is not routinely applicable in acute stroke treatment. Lately, the so-called dynamic cerebral autoregulation (DCA) approach has evolved.[5] It makes use of minor short-term blood pressure changes induced, eg, by deflation of thigh cuffs around the legs or analyses spontaneously occurring fluctuations in ABP. Cerebral perfusion is hereby continuously monitored via cerebral blood flow velocity measured by transcranial Doppler sonography. The noninvasive DCA method is believed to describe similar but not necessarily identical physiological control mechanisms than those for static autoregulation. Whereas both methods are generally convergent in volunteers[6] and after head injury,[11] it has been postulated that DCA may be more sensitive to cerebral hemodynamic impairment.[6] So far, a global bihemispheric impairment of DCA in acute and subacute stroke with preserved static autoregulation has been found.[7]

Two key approaches to analyze DCA from spontaneous oscillations of ABP and CBFV refer to the frequency domain (cross-spectral or transfer function analysis[8,9]) and the time

TABLE 1.   Clinical and Hemodynamic Characteristics

	Study 1 (n=33)	Study 2 (n=29)
Age (SD; range)	61 (12; 18–78)	59 (12; 18–75)
Sex, M:F	23:10	20:9
Time since onset, h (SD; range)	22 (11; 4–48)	134 (25; 72–171)
NIHSS	4.5 (3.8; 0–15)*	2.4 (2.7; 0–10)‡
Treatment prior to study 1		
Heparin or ASS, no.	30	
i.a. thrombolysis, no.	3	
Infarct size on CT or MRI		
>35% MCA territory, no.	1	
>15–35% MCA territory, no.	15	
≤15% MCA territory, no.	7	
No demarcated lesion on initial CT, no.	10	
MCA mean CBFV (cm/s)		
Affected side (SD; range)	39 (18; 12–85)	49 (14; 15–85)†
Unaffected side (SD; range)	40 (13; 16–65)	47 (13; 19–69)†
Mean ABP, mm Hg (SD; range)	86 (12; 65–107)	82 (14; 55–108)
Heart rate, beats/min (SD; range)	68 (13; 48–102)	68 (14; 48–95)
P_{etCO2}, mm Hg (SD; range)	40 (3; 34–47)	39 (3; 32–44)
Clinical outcome		
Good, no. (modified Rankin scale 0–2)		28
Poor, no. (modified Rankin scale ≥3)		1

*National Institutes of Health Stroke Scale (NIHSS) on admission was 5.9 (4.4, range, 0–18). †$P<0.01$, ‡$P<0.001$ between study 1 and 2. No other significant differences between sides and studies were found. Heart rate and P_{etCO2} in controls did not significantly differ from patients. Mean ABP in controls (76 [11] mm Hg) was significantly lower ($P<0.01$) than in patients only at study 1.

domain (correlation coefficient index).[10] Though these approaches have been successfully applied in several studies in patients with head injury and various cerebrovascular diseases,[10–15] they have not been used to detect autoregulatory disturbance in patients with acute cerebral ischemia until now.

This study investigates (1) whether dynamic cerebral autoregulation assessed from spontaneous blood pressure fluctuations is impaired in patients with acute cerebral ischemia and (2) if there is a temporal course of dynamic autoregulatory impairment within the acute stage of cerebral ischemia.

Subjects and Methods

After approval by the local ethics committee and obtaining informed consent, 40 patients admitted to our stroke unit with acute cerebral ischemia were prospectively studied by 2 serial measurements in the acute stage. Inclusion criteria were signs of anterior circulation ischemia, the absence of relevant obstructive carotid artery disease and a sufficient bilateral temporal bone window for insonation of the middle cerebral artery. During the first 48 hours, all patients underwent regular monitoring of ABP, heart rate, and neurological status. Transcranial Doppler/duplex sonography (HDI 3500; ATL) and a clinical examination were performed before each cerebral autoregulation measurement. The first autoregulation study was performed within 48 hours. The second study was performed on day 4 to 7 after ictus. Of the 40 patients, 5 patients were excluded because of Doppler and Finapres measurement artifacts, respectively; 2 patients showed vertebrobasilar ischemia on later MRI and 4 patients did not undergo the second measurement (refusal to attend in 3, transferal to remote hospital in 1). Overall, 33 patients were

eligible for study 1 and 29 patients were eligible for study 2 (Table 1). CT or MRI was performed in every patient. In 23 patients, acute stroke in the territory of the middle cerebral artery could be demonstrated. In 10 patients, no clear infarction could be demonstrated on early CT, but 9 of them had a clinical syndrome consistent with the middle cerebral artery (MCA) territory (ie, sensorimotor+cortical signs like aphasia). Antihypertensive medication was present in 18 of 19 patients at study 1 and 2, and antihypotensive medication (cafedrine+theodrenaline) was found in 7 patients at study 1. The modified Rankin scale was assessed in the 31 patients completing study 1 and 2 after 4±2 months either clinically or by telephone interview. As a control group, 25 age- and sex-matched subjects (age 61±13 years) with no history of previous stroke or significant (>30%) carotid obstruction on carotid ultrasound were recruited from our outpatients clinic. All data of right and left sides from controls were pooled.

Assessment of Dynamic Cerebral Autoregulation

Measurements were performed with subjects in a supine position with moderate elevation of the upper body. Cerebral blood flow velocity (CBFV) was measured in both MCAs by insonation through the temporal bone window with 2-MHz transducers attached to a headband (DWL-Multidop-X; Sipplingen). Continuous noninvasive ABP recording was achieved via a servo-controlled finger plethysmograph (Finapres 2300; Ohmeda) with the subject's right hand positioned at heart level. End-tidal CO_2 partial pressure (P_{etCO2}) was measured in mm Hg with an infrared capnometer (Normocap; Datex) during nasal expiration. P_{etCO2} values were shown to correlate closely with intra-arterial CO_2 values.[16] After stable values had been established, the servo mechanism of the Finapres device was turned off and a data segment of 10 minutes was recorded at a sampling rate of 100 Hz (TurboLab V4.3; Bresser Electronic). The further analyses were performed with a data analysis program (Glance; Seleon
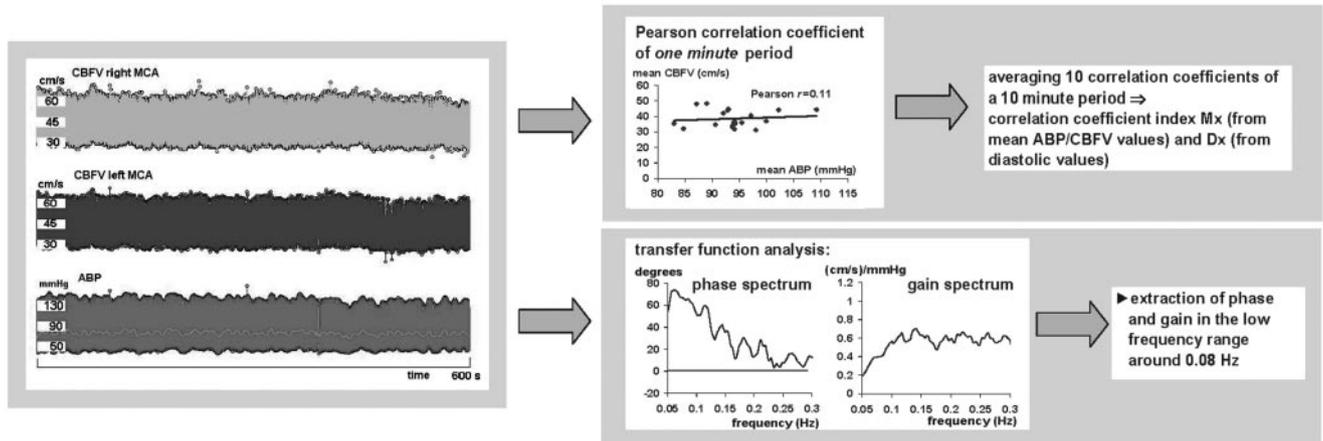
Figure 1. Illustration of dynamic cerebral autoregulation analysis. Sixty-nine-year old man with acute left-sided parietal ischemia. Example represents autoregulation analysis from mean ABP and CBFV in the left-middle cerebral artery. The shown low correlation coefficient indicates independence of CBFV from ABP changes as a sign of intact autoregulation. A more positive correlation would indicate dependence of CBFV from ABP attributable to autoregulatory impairment. The phase and gain spectra represent high-pass filter properties of the intact cerebral autoregulatory feedback control system, ie with increasing frequency the filtering effect (existing phase shift or reduced gain) is diminishing.

GmbH) and custom-written software developed in-house. The mean length of time series analyzed was 587 ± 61 seconds. Mean CBFV in both MCAs, ABP, heart rate, and P_{etCO2} was assessed over a period of 2 minutes at the beginning of each measurement.

Correlation Coefficient Analysis

This method has been described in more detail previously.[15] In short, diastolic and mean values of ABP and CBFV were averaged over 3 seconds. Consecutively, from every 20 such values (ie, 60-second periods), separate Pearson correlation coefficients between mean ABP and CBFV were calculated. The resulting sets of 1-minute correlation coefficients were then averaged yielding the autoregulatory index Mx (Figure 1). There were no ABP trends or sustained changes in the 1-minute windows and ABP showed a variance of 3% to 8% with an average period of ≈ 10 seconds.

Transfer Function Analysis

This method has been outlined in more detail previously.[17,18] In brief, power spectra S_{ABP}, S_{CBFV}, and the cross-spectrum CS were estimated by transforming the time series of ABP and CBFV with discrete Fourier transformation to the frequency domain. Smoothing the respective periodograms resulted in the power spectra and CS estimates. With the smoothing used (triangular window of half-width 8 frequency bins), the coherence (normalized modulus of CS) is significant at the 95% level if it exceeds 0.49. The phase spectrum is the argument of the cross-spectrum, the gain can be interpreted as the regression coefficient of CBFV on ABP. Phase shift and gain in the low frequency (LF) range (LF phase, 0.06 to 0.12 Hz) were extracted using previously specified rules, the most important of which is to select a point of high coherence within the respective frequency range.[17]

Statistical Analysis

Calculation of intra-individual and interindividual differences and correlations was performed using nonparametric tests (Wilcoxon, Mann–Whitney, Kruskal–Wallis). We report nominal probability values not adjusted for multiple comparisons. $P < 0.05$ was considered statistically significant. Although nonparametric tests have been used, for reasons of clearness data are reported mainly as mean (SD), but main results are also illustrated as box-and-whisker plots.

TABLE 2. Indices of Dynamic Cerebral Autoregulation in Patients With Acute Ischemic Stroke and Healthy Controls

	Stroke Patients Study 1 (n=33)		Study 2 (n=29)		
	Affected Sides	Unaffected Sides	Affected Sides	Unaffected Sides	Controls (n=25)
Correlation coefficient method					
Mx	0.19 (0.18)	0.19 (0.18)	0.27 (0.16)*	0.25 (0.15)*	0.20 (0.13)
Side-to-side difference	0.00 (0.11)		0.02 (0.08)		± 0.02 (0.06)
Transfer function analysis					
Phase shift in degrees (LF range)	44 (20)	49 (20)	39 (19)	45 (23)	48 (15)
Side-to-side difference	-5.1 (22.3)		-6.6 (12.4)		± 1.5 (7.7)
Gain in (cm/s)/mm Hg (LF range)	0.57 (0.24)	0.58 (0.20)	0.64 (0.23)	0.67 (0.29)	0.60 (0.20)
Side-to-side difference	-0.01 (0.24)		-0.02 (0.18)		± 0.04 (0.14)

LF indicates low frequency. *$P < 0.05$ between study 1 and 2. Side-to-side differences represent absolute values calculated as affected side minus unaffected side. For transfer function analysis, due to insignificant coherence, 5 patients had to be excluded from study 1, 3 patients from study 2. Control values were pooled from all left and right sides. One control side was excluded because of Doppler artifacts.
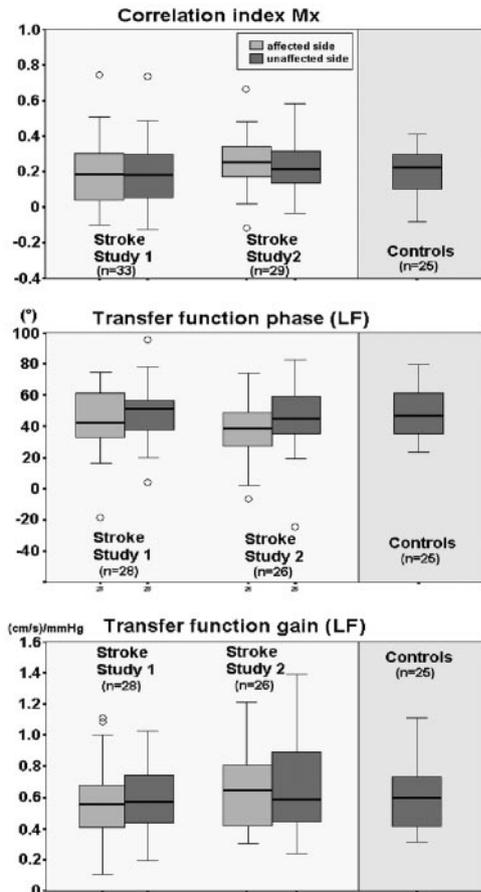
Figure 2. Box-and-whiskers plots of autoregulatory indices in acute ischemic stroke. Bars denote medians, boxes denote interquartile ranges, whiskers denote ranges excluding statistical outliers (○) (>1.5 box lengths from either the twenty-fifth or seventy-fifth percentiles). For significances see Table 2. The *n* for transfer function parameters is reduced attributable to insignificant coherence in few patients.

Results

Clinical and hemodynamic characteristics are given in Table 1. Figure 1 illustrates the methods used for graduation of dynamic cerebral autoregulation from spontaneous oscillations in ABP.

Results for autoregulation indices are given in Table 2. Ranges are plotted as box-and-whiskers in Figure 2. Overall, no clear disturbance of dynamic cerebral autoregulation was indicated by the different parameters in comparison to controls. Values of Mx index in study 2 were slightly but significantly greater than in study 1, indicating worse autoregulation later after stroke. Also, LF phase showed a nonsignificant tend toward poorer values on affected sides at study 2 (Figure 2). Separate analyses for clinical severity (National Institutes of Health [NIH] at study 1: <4, n=17; ≥4, n=16), stroke side (left, n=20; right, n=13), verification of demarcated MCA lesion on CT/MRI (yes, n=23; no, n=10), size of infarction (≥25% MCA territory, n=14; <25%, n=9; average size, 21 [7]%) did not reveal relevant differences for the various autoregulatory indices on affected sides at study 1 and 2.

Discussion

This study did not show a *major* disturbance of dynamic autoregulation in acute ischemic stroke. For interpretation of the study results, the expected nature of autoregulatory impairment in acute stroke and its methods of detection are pivotal.

From a hemodynamic view, CBFV fluctuations might well reflect relative changes in cerebral blood flow,[19] but the insonation of the MCA main stem represents a large area of downstream arterioles. This renders detection of possible *localized* autoregulatory impairment in smaller infarcted areas unlikely. Also, autoregulatory impairment in distinctive collaterals of the penumbra might not be detected unless they represent a relevant part of the remaining MCA flow. Thus, the present investigation extends to a more generalized impairment of autoregulatory disturbance, at least in the vessel territory in which the infarcted area lies.

A basic limitation of this investigation is that either CT or MRI with their different sensitivities has been used for confirmation of ischemia, and the ischemic area itself could not be confirmed on early CT imaging in 10 of the studied patients. Nearly all of these patients had a clinical syndrome consistent with the MCA territory and a benign course with rapid recovery of symptoms within a few days. It should also be noted that grouping only on clinical severity by the NIH score could be misleading, because a small deficit in the area of internal capsule might result in *higher* NIH score than an extended cortical lesion. Nonetheless, the overall *low* NIH scores in the present patients and the small infarcts in confirmed strokes on imaging support the presence of a minor stroke population with predominantly small MCA infarctions.

Previous studies analyzing dynamic autoregulation in *acute* territorial and lacunar stroke within 72 to 96 hours by the cuff inflation/deflation method or manually selected spontaneous ABP transients[7,20,21] found a modest impairment of dynamic but not static autoregulation in *both* MCAs, which was unrelated to stroke severity and lasted for at least 1 to 2 weeks.[20] Because the studied cohort also comprised posterior circulation events, a global impairment of DCA was assumed and the known autonomic dysfunction after stroke was suggested to play a role for this phenomenon.[7] It is important that the present *first* measurement point (study 1) was generally restricted to an *earlier* stroke stage than in these studies. The intraindividual *time course* of static or dynamic autoregulatory disturbance has not been extensively studied in humans during the first days after cerebral ischemia. Interestingly, in animal models myogenic autoregulatory activity after MCA occlusion was reduced only after a *longer* period of reperfusion.[22] If the present results could be interpreted in favor of autoregulatory disturbance during acute stroke, then study 2 showed a trend toward poorer autoregulatory values (Figure 2). This measurement point might correspond more closely to that of the previous studies showing modest dynamic autoregulatory disturbance.[7,21,23] Therefore, the idea of delayed generalized autoregulatory disturbance in temporal association with the period of hyperperfusion (note the significant greater MCA flow velocities on both sides at study 2) and cytotoxic edema merits further attention in future studies.
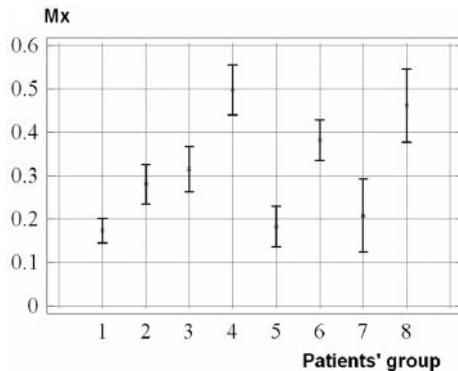
Figure 3. Overview on Mx values in different pathological and physiological situations from previous studies. Bars indicate mean and 95% confidence limits. Patient groups: 1 and 2 head injury patients (n=187) with survival (1) or death (2)[32], 3 and 4: carotid artery stenosis (n=71), uni- (3) or bilateral (4)[33], 5 and 6: young volunteers (n=47) under normo- (5) and hypercapnia (6)[34], 7 and 8: SAH patients (n=15) before (7) and during (8) vasospasm.[5] Mx was calculated for consistency using mean CBFV and ABP; in head injured patients, or in other cases where intracranial pressure may be elevated, cerebral perfusion pressure is more appropriate.

The validity and precision of the *methodology* used to detect dynamic autoregulatory impairment also requires close attention. We used 2 widely applied approaches for extracting dynamic autoregulatory information from spontaneous blood pressure oscillations.[9,12,13,15,24–27] The *transfer function phase* is based on a high-pass filter model on dynamic cerebral autoregulation (Figure 1) and it is generally accepted as an index of dynamic cerebral autoregulation. It can be explained as a continuous early counter-regulation of CBFV to increases/decreases in ABP causing a lead of the respective maximum/minimum of CBFV in relation to ABP in an oscillating system. Clearly, disturbed autoregulation is indicated by a diminished phase shift of $<15°$ to $20°$,[8,9,15] and such values have been primarily found in poorly compensated critical carotid or MCA stenosis[9,13,28] or vasospasm after subarachnoid hemorrhage (SAH),[11] but also in eclampsia.[29] The sensitivity of phase shift with regard to detection of a given autoregulatory impairment has not been investigated so far and data comparing it to the cuff deflation method in pathophysiological situations are missing. Although the use of spontaneous changes in ABP as a stimulus bears advantages with regard to patient cooperation and tolerance, it will generally yield more noise in the results than using the more precise but less comfortable stimulus of cuff deflation. The relatively wide scattering of phase shift values thus might not have clearly detected a comparatively slight or relative disturbance of dynamic cerebral autoregulation particularly in the early study.

The pathophysiological behavior of *transfer function gain* is less well understood. Being principally also based on the high-pass filter system, it reflects in a static sense the amplitude dampening of slow ABP fluctuations, and increasing gain should indicate less filtering with more direct transmission of amplitude changes and thus poorer autoregulation. In case of an upstream stenosis, however, it is paradoxically reduced,[17] probably because of the direct he-

modynamic effect of the stenosis. The present results of transfer function gain in acute stroke patients were in the range reported for healthy adults in various recent studies and did not differ between sides and measurements.[25,30,31] Larger clinical data on acute cerebrovascular diseases with clearly increased (ie, impaired) gain are lacking so far; therefore, this parameter should be interpreted with caution.

The *correlation coefficient method*, which indicates the independence of accurately autoregulated cerebral blood flow from ABP by absent correlations, has been applied to various cerebral diseases (Figure 3). It seems that not a general type of pathology (like head injury or SAH) but a severe obstructive vascular factor (like vasospasm or bilateral carotid stenosis, also complications leading to death in head injury) causes poor Mx values. Patients with severe upstream carotid obstruction thus were not included in the present study. Furthermore, the strong dependence of autoregulation on P_{aCO_2} levels has to be considered. The patients and controls presently studied were normocapnic, and a significant influence of P_{etCO_2} on the basic findings thus seems unlikely. The Mx may reflect both static and dynamic components of autoregulation, depending on the temporal course of blood pressure. In the present patients, ABP fluctuated dynamically (see Subjects and Methods), and the Mx thus contains information about dynamic autoregulation predominantly.

Overall, the applied parameters derived from spontaneous changes in ABP and CBFV did not indicate a relevant impairment of dynamic autoregulation *early* after *minor* ischemic stroke, whereas a slight autoregulatory disturbance in the *subacute* stage might be present. This supports the view that infarction in a smaller downstream area does not lead to a relevant early generalized arteriolar dysfunction in the whole ipsilateral or remote vessel territories but that during the subacute stage such a condition may occur at least in the affected vessel territory. It should be noted that negative (nonsignificant) results do not prove a lack of association by themselves. We did not perform prespecified power calculations for detection of autoregulatory impairment and thus we can only regard these results as proof on subjective judgment.

In the end, the question remains whether noninvasive assessment of DCA in acute stroke deserves a future role in clinical research and routine. Given the present results, focus should be on larger MCA strokes, particularly in the subacute reperfusion or hyperperfusion state after primary MCA occlusion (also that after thrombolysis). Knowledge of DCA behavior in individual cases might contribute to optimized blood pressure strategies in that stage. Larger prospective studies, including poor-grade strokes, should be conducted to investigate a possible link between autoregulation and outcome in stroke.

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