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Cerebral Autoregulation Dynamics in Acute Ischemic Stroke after rtPA Thrombolysis

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Key Words
Cerebral autoregulation · Acute cerebral ischemia · Thrombolytic therapy · Recombinant tissue plasminogen activator · Transcranial Doppler sonography

Abstract
Background: To investigate whether there is: (1) a specific temporal course of cerebral dysautoregulation in acute ischemic stroke, and (2) a separate detrimental effect of recombinant tissue plasminogen activator (rtPA) on autoregulation dynamics in this situation. ***Methods:*** We studied 16 patients with acute middle cerebral artery (MCA) occlusion and rtPA thrombolysis (intra-arterial or intravenous application, or both). Controls were 71 healthy adults and 11 patients with minor stroke not receiving rtPA. Dynamic autoregulation was recorded from spontaneous fluctuations of blood pressure and MCA flow velocity (transcranial Doppler) using two well-described approaches (index Mx, phase shift). Three measurements were performed (study 1: 20 ± 9 h of ictus; study 2: 64 ± 10 h; study 3: 112 ± 7 h). ***Results:*** Two groups of clinical outcome were identified: good (modified Rankin scale ≤2, n = 9, MCA infarct volume = 14 ± 16%), poor (modified Rankin scale >2, n = 7, MCA infarct volume = 62 ± 21%). In the good outcome group, no relevant changes in Mx and phase were observed on both MCA sides compared with controls. In the poor outcome group, the index Mx deteriorated over studies 1–3 on affected sides, with worse values compared to the controls ($p < 0.05$). Phase was already impaired on affected sides of poor outcome patients in study 1 ($p < 0.01$ vs. controls) and tended to decrease further until study 3. Phase also decreased moderately on contralateral sides in poor outcome patients from studies 1 to 3 ($p < 0.05$, nonsignificant compared with controls). ***Conclusions:*** Cerebral autoregulation is increasingly impaired, mainly on the affected side, over the first 5 days of major ischemic stroke after unsuccessful rtPA thrombolysis. It is bilaterally preserved in minor stroke after successful rtPA thrombolysis, indicating no separate detrimental effect of rtPA on the cerebral autoregulatory mechanism.

Introduction

Clinical guidelines on blood pressure treatment in acute ischemic stroke often refer to pathophysiological assumptions regarding potential cerebral autoregulatory disturbances [1, 2].

During the initial stages of vessel occlusion and early reperfusion, tissue lactate acidosis leads to local vasoparalysis compromising the autoregulatory mechanism in the ischemic core, and also by diffusion in the direct periinfarct region [3]. In addition, experimental studies suggest that free oxygen radicals generated during further reperfusion in postischemic tissue may lead to microvas-

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cular injury and secondary autoregulatory failure [4]. Consistently, decreased myogenic reactivity in animal cerebral arteries has been shown to occur, only delayed, after reperfusion [5]. Thus, impaired autoregulation in this later stage may contribute to reperfusion injuries with hyperperfusion and postischemic edema [6, 7]. There is, however, little information about whether such a time course of potential cerebral dysautoregulation occurs during the acute stage of reperfused ischemic stroke in humans.

Attempting early recanalization with recombinant tissue plasminogen activator (rtPA) is the treatment of choice in acute intracranial vessel occlusion [8]. Interestingly, an in vitro analysis of postischemic animal cerebral arteries showed that reperfusion with rtPA exhibits an additive vasotoxic effect with clearly diminished myogenic arterial reactivity [9]. Thus, thrombolysis with rtPA may additionally impair the cerebral autoregulatory mechanism, and consequently contribute to reperfusion injury and inherent hemorrhagic complications. In a previous clinical study, thrombolysis with streptokinase led to an increased frequency in subsequent luxury perfusion with poorer functional outcome [10]. The actual in vivo effect of thrombolytic treatment with rtPA on the course of cerebral autoregulation in reperfused acute ischemic stroke is unknown.

Serial assessment of autoregulatory ability in an acute clinical situation has been considered difficult because of the need for potentially harmful blood pressure changes. This situation has now been changed by the introduction of dynamic autoregulatory methods using spontaneously occurring blood pressure fluctuations as autoregulatory stimuli [11–13].

The present clinical study investigates whether there is: (1) a specific temporal course of cerebral dysautoregulation in the acute stage of ischemic stroke after vessel reperfusion, and (2) a specific detrimental effect of rtPA on autoregulation dynamics in this situation.

Subjects and Methods

Patients

We prospectively studied 18 patients admitted to our stroke unit with acute middle cerebral artery (MCA) occlusion between October 2005 and January 2007. Inclusion criteria were: (1) clinical signs of major anterior circulation stroke on admission [National Institute of Health stroke score (NIH-SS) ≥10], (2) confirmation of acute ischemia and MCA occlusion on diffusion-weighted magnetic resonance imaging and magnetic resonance angiography, or early ischemic signs on computed tomography plus signs of MCA occlusion on transcranial Duplex sonography, and (3) thrombolytic treatment with rtPA (intravenous, intra-arterial or combined application, i.e. 'bridging' approach). Exclusion criteria were a significant persistent internal carotid artery obstruction (≥70%) on either side at the time of autoregulation studies and an insufficient bilateral temporal bone window for insonation of the MCA. The study had been approved by the local ethics committee and written informed consent was obtained from all patients or relatives.

Study Protocol

The measurement protocol consisted of 3 autoregulatory measurements within the first 5 days (120 h) after stroke onset: study 1 at 12–24 h, study 2 at 60 ± 12 h, and study 3 at 108 ± 12 h. If no MCA recanalization was observed at the time of study 1, a short term follow-up after 6–24 h was performed to complete study 1.

Clinical and Neuroimaging Data

During the study period, all patients underwent regular monitoring of the arterial blood pressure (ABP), heart rate, temperature, blood glucose level and neurological status according to the local stroke unit's standard procedures. Blood pressure management was based on the current European criteria for stroke management guidelines [2], and performed by stroke physicians not involved with the study and unaware of any autoregulation data. All patients received standard medication in various combinations including antihypertensive or pressor agents, statins, antithrombotic and antibiotic medication. Transcranial Doppler sonography (TCD) and a clinical examination [assessment of NIH-SS and modified Rankin Scale (mRS)] were performed prior to each autoregulation study and at hospital discharge. The volume of MCA infarction was estimated by one rater (A.H.) blinded to any autoregulation data from early follow-up images (CT or MRI) in all but 1 patient, in whom only the initial MRI could be assessed (diffusion-weighted image lesion then considered).

Control Groups

Reference autoregulation values were obtained from 71 age-matched persons (64 ± 9 years) out of our previously studied control person pool. No control subject had a history of cerebrovascular disease or any carotid obstruction on their duplex scan. As an rtPA-naïve control group with minor stroke, 11 patients were taken from a previously studied cohort [13]. These patients were matched to study 1 of the 'good' rtPA outcome group (see 'Results, Clinical Course') with regard to size of infarction (18 ± 10% of MCA territory), age (62 ± 7 years), stroke severity (NIH stroke score 5 ± 4 at autoregulation study) and duration of ischemia (23 ± 12 h).

Assessment of Hemodynamic Data

Measurements were performed with subjects in a supine position with slight to moderate elevation of the upper body. Cerebral blood flow velocity (CBFV) was measured in both MCAs by TCD with 2 MHz transducers attached to a head frame (TC2-64, EME, Germany). Continuous ABP recording was achieved via a servo-controlled finger plethysmograph (Finapres, USA). ABP was additionally assessed with a standard oscillometric technique applying a cuff to the patients' upper arms. End-tidal CO_2 partial pressure (P_{ETCO_2}) was measured in mm Hg with an infrared capnometer (Normocap Datex, Finland) during nasal expiration. Af-

Table 1. Clinical characteristics

	All patients (n = 16)	Good outcome (n = 9)	Poor outcome (n = 7)	p value
Age, years	67 ± 12	64 ± 14	72 ± 6	0.299
Female/male	7/9	5/4	2/5	0.126
NIH-SS on admission	14 ± 3	13 ± 3	16 ± 2	0.016
Affected hemisphere (right/left)	9/7	6/3	3/4	0.358
MCA status on admission				
M1 occlusion	14	7	7	0.175[1]
M2 or M3 occlusion	2	2	0	
rtPA treatment				
i.v. only	5	4	1	0.106[2]
i.a. only	2	2	0	
i.v./i.a. combined	9	3	6	
Dose, mg	68 ± 8	66 ± 6	72 ± 10	0.252
Event-to-treatment time, h	2.3 ± 1.0	2.4 ± 1.2	2.2 ± 0.5	0.918
Volume final infarction, %MCA	37 ± 28	14 ± 6	62 ± 21	<0.001
Hypertension	11	6	5	0.798
Diabetes mellitus	4	1	3	0.088
Current smoking	3	1	2	0.213
Statin-treated dyslipidemia	5	4	1	0.106

Values are mean ± SD where appropriate. The p values indicate significances between good and poor outcome groups.

[1] Comparison of proportion M1 versus M2/3 between groups.

[2] Comparison of intravenous (i.v.) only versus intra-arterial (i.a.) with or without previous i.v. application of rtPA.

ter establishing stable values, a data segment of 10 min was recorded with the patients breathing spontaneously.

Analysis of Autoregulation

We used two previously described methods to quantify cerebral autoregulation dynamics, which make use of spontaneously occurring fluctuations in ABP and CBFV [12–14]: (1) correlation coefficient analysis: this approach is based on the simple assumption that decreasing cerebral autoregulation leads to an increasing correlation between fluctuations in CBFV and ABP (i.e. CBFV depends increasingly on fluctuations in ABP). To quantify this correlation, mean values of ABP and CBFV raw data were first averaged over 3 s. Consecutively, from every 20 such 3-second averages (i.e. from 1-min periods), Pearson's correlation coefficients between the mean ABP and CBFV were calculated (see fig. 2 for examples of different 1-min correlation coefficients). The resulting sets of 1-min correlation coefficients gained from the whole time series were then averaged, yielding the autoregulatory index Mx; (2) transfer function analysis (also called cross-spectral analysis): this frequency domain method calculates the phase shift between the input signal (ABP) and output signal (CBFV). The phase shift itself is a measure of the extent to which each frequency component of the respective CBFV time series leads the ABP time series. This phase lead probably arises from continuous early counter-regulation of CBFV against repetitive rise and falls in ABP [16]. Thus, it vanishes with decreasing dynamic autoregulatory capacity. Note that, mathematically, the phase shift is actually negative because the CBFV (output signal) leads the oscillations of ABP (input signal), but that it is usually given as a positive number (i.e. inverted). In more detail, the phase shift was calculated by first estimating the power spectra of ABP and CBFV and their cross-spectrum by transforming the time series of ABP and CBFV with discrete Fourier transformation to the frequency domain. From the cross-spectrum, the phase spectrum was derived (see fig. 2 for examples of phase spectra). In the present analysis, the phase shift was determined for both MCA sides from the low-frequency range (0.06–0.12 Hz, Mayer waves) by averaging the values at all frequency bins where the coherence was significant (>0.49) [17].

The short-term reproducibility of the applied dynamic autoregulation methods Mx and phase is moderate to good in case of good insonation conditions [18], which were a prerequisite for inclusion into the present study.

Statistical Analysis

Comparisons between patient groups and study points and calculation of intra-individual differences were performed using nonparametric tests (Wilcoxon test, Friedman test, Mann-Whitney U test, Kruskal-Wallis test for continuous variables; Fisher's exact test for categorical variables). We report nominal p values, not adjusted for multiple comparisons, considering p values of <0.05 statistically significant.

Table 2. Course of clinical and hemodynamic status during autoregulation studies 1–3

	Study 1 (n = 16)	Study 2 (n = 15)	Study 3 (n = 15)	p values (between studies)
Time since onset, h				
All	20 ± 9	64 ± 10	112 ± 7	
Good outcome	17 ± 7	61 ± 10	107 ± 6	
Poor outcome	23 ± 10	69 ± 10	115 ± 8	
p values between outcomes	0.252	0.142	0.031	
NIH-SS				
All	14 ± 3	8 ± 7	7 ± 7	<0.001
Good outcome	6 ± 5	3 ± 3	3 ± 3	<0.001
Poor outcome	16 ± 2	16 ± 3	15 ± 3	0.035
p values between outcomes	<0.001	<0.001	<0.001	
Mean ABP, mm Hg				
All	94 ± 12	93 ± 15	94 ± 10	n.s.
Good outcome	92 ± 11	92 ± 12	94 ± 10	n.s.
Poor outcome	96 ± 14	94 ± 19	94 ± 11	n.s.
p values between outcomes	0.536	0.955	0.864	
P_{CO2} end-tidal, mm Hg				
All	35 ± 4	34 ± 4	34 ± 4	n.s.
Good outcome	35 ± 3	36 ± 3	36 ± 3	n.s.
Poor outcome	34 ± 4	32 ± 3	32 ± 3	n.s.
p values between outcomes	0.536	0.088	0.113	
MCA mean CBFV affected side, cm/s				
All	57 ± 21	66 ± 26	61 ± 23	n.s.
Good outcome	62 ± 16	74 ± 23	70 ± 17	n.s.
Poor outcome	50 ± 25	55 ± 27	57 ± 11	n.s.
p values between outcomes	0.299	0.299	0.145	
MCA mean CBFV unaffected side[1], cm/s				
All	52 ± 16	57 ± 22	55 ± 21	0.038
Good outcome	57 ± 17	66 ± 17	63 ± 17	n.s.
Poor outcome	44 ± 11	46 ± 25	53 ± 12	n.s.
p values between outcomes	0.142	0.091	0.113	

Study 3 was performed slightly but significantly later in the poor outcome group, but it is not believed to explain the heterogeneity in autoregulation results. The n values at studies 2 and 3 are reduced because 1 patient died on day 4. n.s. = Nonsignificant.

[1] No significant differences between affected and unaffected MCA side.

Results

Clinical Course

Baseline characteristics of the final 16 rtPA patients analyzed are given in table 1. Two patients had to be excluded from further analysis because of Doppler artifacts in at least 1 of the 3 autoregulation recordings. Overall, 9 of the 16 patients had a benign course with a good clinical outcome (mRS 0–2) and small infarction, while 7 patients had a poor clinical outcome (mRS 3–6) with a larger infarction. One of the latter died on day 4 due to malignant MCA infarction in combination with additional contralateral traumatic brain hemorrhage, another patient died on day 7 due to malignant MCA infarction with massive brain edema. This patient underwent monitoring of intracranial pressure with an ipsilateral parenchymal probe yielding a cerebral perfusion pressure of >90 mm Hg at both study 2 and 3. Table 2 summarizes the course of general hemodynamic and clinical status over the 3 autoregulatory studies.

Course of Cerebral Autoregulation

MCA recanalization as a prerequisite for Doppler monitoring and autoregulation testing was present in 14

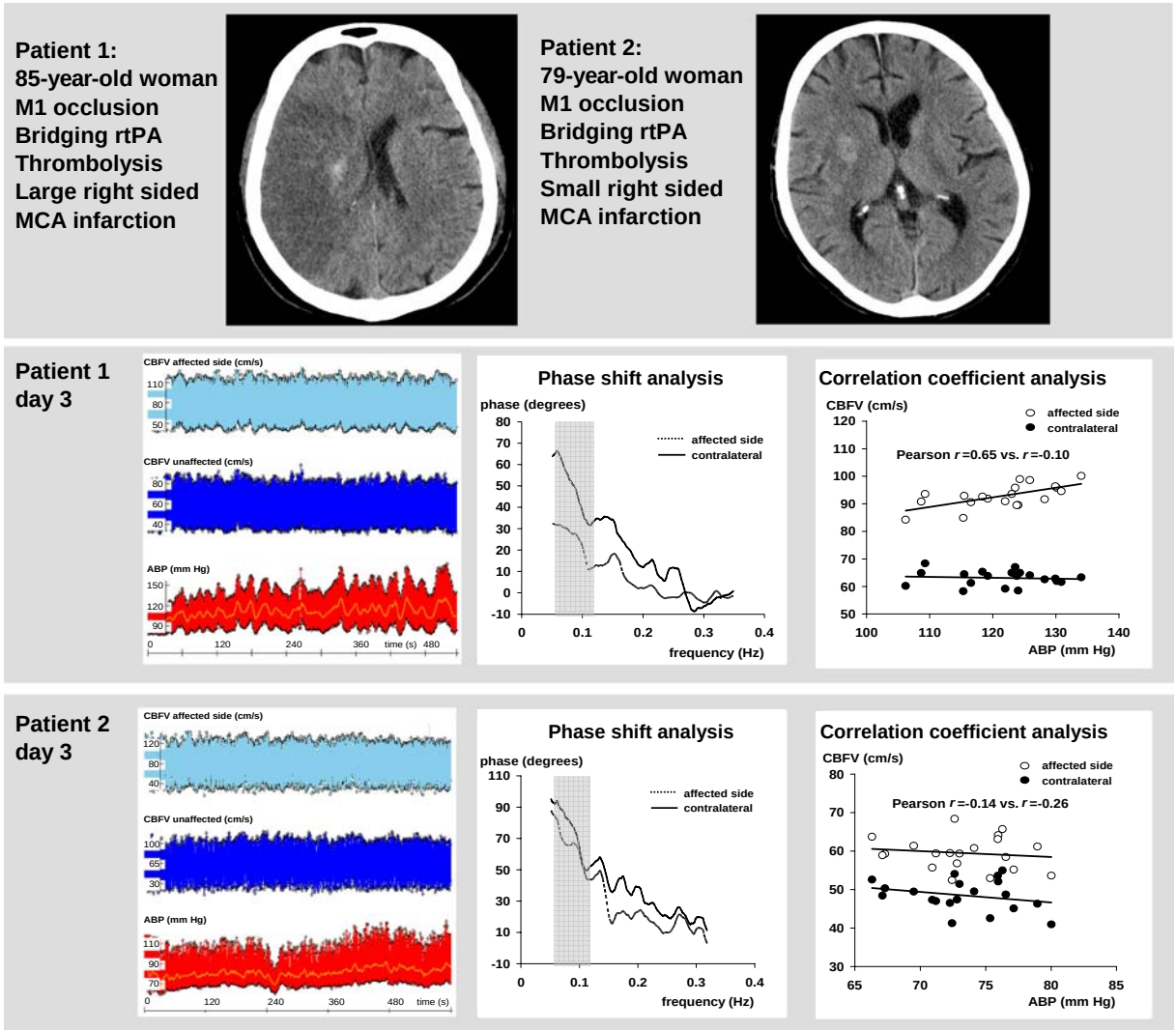

Fig. 1. Illustrative recordings. Patient 1: autoregulation study shows a lower phase shift between slow oscillations of ABP and CBFV on the affected side (0.06–0.12 Hz). The 1-min correlation coefficient example shows a positive correlation between ABP and CBFV fluctuations on the stroke side of the MCA (the index Mx is formed by averaging such consecutive 1-min correlation coefficients over the whole time series). Patient 2: autoregulation measures show intact phase shift and no positive correlation, both on the affected and unaffected sides, indicating preserved autoregulation. The hyperintense signal on both CT scans was interpreted as the contrast agent.

of 16 patients at the first attempt of study 1. Two patients showed recanalization on short term follow-up after 6 and 24 h. Figure 1 illustrates autoregulation analysis in 2 individual patients with different outcomes. Group results are shown in figure 2. In patients with successful thrombolysis and a small infarction, cerebral autoregulation was not altered in comparison with rtPA-naïve minor stroke patients and healthy controls. Conversely, in patients with poor outcome and large MCA infarction, the index Mx increased (i.e. deteriorated) from study 1 to 3 on affected sides resulting in significantly worse values compared with controls at study 3. Phase was significantly impaired on affected sides at study 1 and also tended to decrease until study 3. On contralateral sides, phase decreased significantly in patients with poor outcome from study 1 to 3.

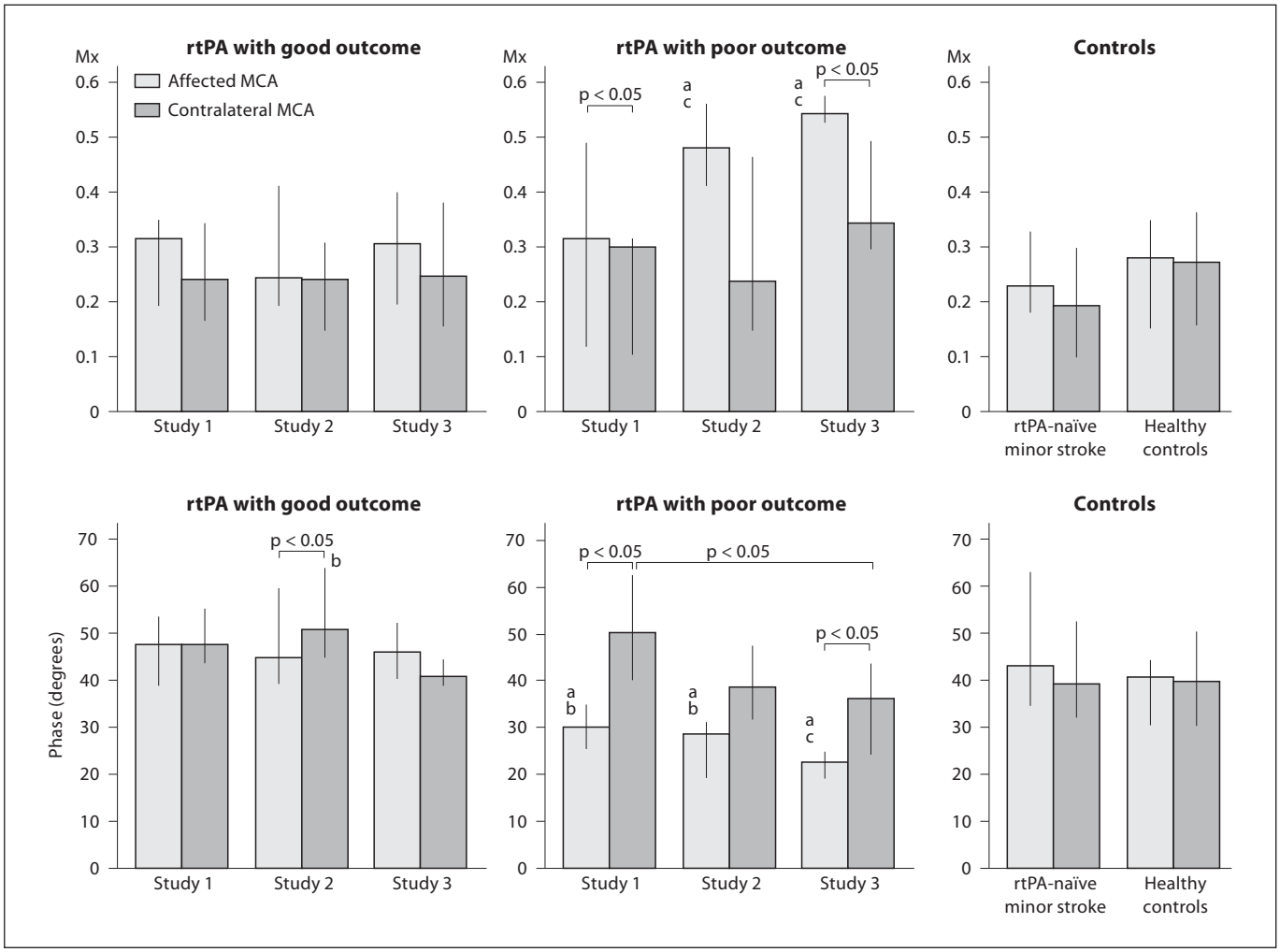

Fig. 2. Course of autoregulatory indices (Mx and phase) in acute MCA stroke. Patients after rtPA thrombolysis with good outcome and small infarction (n = 9) and poor outcome and large infarction (n = 7). Phase analysis was not possible in 1 patient of the good outcome group because of nonsignificant coherency. Comparison with rtPA-naïve minor-stroke patients (n = 11) and healthy controls (n = 71, right and left MCA). Note that increasing Mx and decreasing phase indicate disturbed autoregulation. [a] $p < 0.05$ (comparison with affected side of good outcome group); [b] $p < 0.05$ and [c] $p < 0.01$ (comparison with healthy controls). Bars represent medians, whiskers denote quartiles.

Discussion

This study shows that cerebral autoregulation is increasingly disturbed in the territory of large ischemic stroke during the first days of vessel reperfusion with rtPA. In contrast, autoregulation remains preserved in patients with reperfused small infarction after successful rtPA thrombolysis.

The concept of dynamic cerebral autoregulation enables noninvasive monitoring of cerebral autoregulation in acute stroke from spontaneous blood pressure fluctuations [13, 17, 19]. Dynamic autoregulation itself also correlates closely with the classical static autoregulation [20]. An important limitation of the applied TCD approach is that it can assess the MCA territory only as a whole. Thus, focal areas of autoregulatory impairment, even within the small infarcted area, after successful thrombolysis cannot be ruled out with the present study. An autoregulatory disturbance affecting relevant parts of the MCA territory should, however, be detected by TCD.

Previous TCD studies found a bilateral disturbance in dynamic autoregulation in the MCA lasting for at least 14 days, independent of the site of stroke (MCA or posterior cerebral artery) and stroke severity [21, 22]. Studies using single photon emission computed (or positron emission) tomography showed that the lower limit of static autoregulation can be impaired in affected territories of hypertensive stroke patients [23, 24]. These important studies measured autoregulation once during the first days of stroke, not allowing the observation of a temporal evolution of dysautoregulation during this period of vessel reperfusion. We previously measured dynamic autoregulation serially 2 and 5 days after minor MCA stroke. It was preserved with a trend towards poorer values on day 5 over both sides [13].

Here, we show that in patients with reperfused large MCA stroke and poor outcome, cerebral dysautoregulation evolves over affected sides as assessed by the index Mx during the first days. A decreasing autoregulatory capacity in the early subacute stage of stroke was also reported in the direct peri-infarct region of poor outcome patients with malignant MCA infarction by invasive monitoring of tissue oxygenation [3]. The presently applied second autoregulatory index phase was already initially impaired in the large-stroke group, but also tended to decrease further. The absolute phase values over affected sides are comparable to those of 10 patients with large MCA infarction examined once within 3 days of onset without reported rtPA treatment [17]. Also, in an early study of the pre-thrombolysis era, static autoregulation was poorer in large compared with mild or moderate hemispheric infarction [25]. Thus, rather the size of infarction than rtPA treatment seems to affect poststroke dysautoregulation. As a limitation of the present study, we did not measure patients without rtPA treatment and subsequent large infarction to corroborate this point.

Yet, the present results do not favor a general sustained detrimental effect of rtPA thrombolysis on autoregulatory ability, since autoregulation remains preserved in minor stroke during the first 5 days after thrombolysis. In comparison with a previous in vitro animal model [9], autoregulation was first assessed 10–20 h after thrombolytic therapy in the present study; thus, not excluding a transient short-lived period of dysautoregulation immediately after rtPA application. Another reason for differing results may be the lower concentration of rtPA active within the vessel wall in the patients studied here. However, many of them received at least a portion of the thrombolytic therapy locally via an intra-arterial catheter, suggesting a relatively high concentration of rtPA active on the vessel wall.

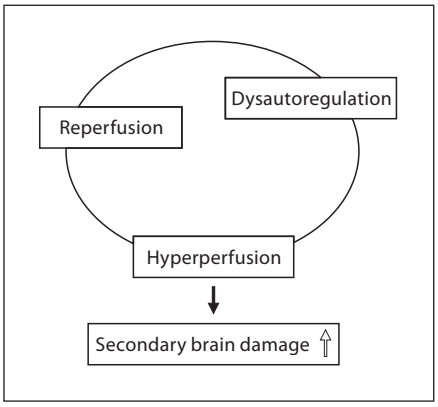

Fig. 3. Suggested vicious circle of reperfusion and cerebral dysautoregulation. Reperfusion leads to secondary vasculopathy by increased local production of free oxygen radicals (e.g. peroxynitrite [4]), which relax cerebral arterioles as the main effectors of cerebral autoregulation. Thus, secondary hyperperfusion may occur due to autoregulatory failure [15], leading to further increased reperfusion with enhanced production of oxygen radicals and further dysautoregulation. The resulting hyperperfusion may then contribute to secondary brain damage with edema and further ischemic injury.

Overall, development of cerebral dysautoregulation may be particular critical during the first days of reperfusion in larger infarctions. This is probably also the most interesting time period with regard to functional brain reorganization [26]. Early postischemic hyperperfusion may be a rather harmless condition, whereas late hyperperfusion with a breakdown of the blood-brain barrier could contribute to secondary ischemic injury [15]. The current results support the theory of an additional secondary autoregulatory failure in acute (large) cerebral ischemia. Cerebral dysautoregulation may therefore play a significant role within the detrimental effect of reperfusion and hyperperfusion [15]. As supposed for malignant MCA infarction [3], a vicious circle may start in the peri-infarct area by spreading local acidosis with consequent dysautoregulation, hypo- or hyperperfusion, edema and further infarction. We suggest a comparable vicious circle emphasizing the role of reperfusion in the evolution of (secondary) autoregulatory failure (fig. 3).

The evolving autoregulatory failure may also be ascribed to a possible raise in intracranial pressure in larger infarction, with cerebral perfusion pressure falling below the lower limit of autoregulation. Arterial blood pressure was maintained at a comparatively high level and

closely monitored in all patients, but intracranial pressure was not regularly measured in the present noninvasive monitoring study. Interestingly, in the 1 patient with most severe edema and poor outcome, cerebral perfusion pressure was >90 mm Hg, both at study 2 and 3, but autoregulation was still very poor. This case favors a separate postischemic dysautoregulation rather than a perfusion pressure problem only.

Disturbed autoregulation in the contralateral hemisphere in acute stroke was reported previously in an in vitro animal study and in humans [5, 27]. Others could not find altered static [28] or dynamic [16] autoregulation in acute major MCA stroke in the contralateral hemisphere. Presently, patients with poor outcome and a large infarction showed a significant trend towards poorer phase values on day 5 on contralateral sides, although absolute values did not differ from healthy controls. Thus, a slight general (i.e. contralateral) autoregulatory impairment may evolve in patients with acute major stroke over the first days.

Finally, translation of present results into clinical practice suggests that special attention should be paid to the early subacute stage of large acute ischemic stroke, when secondary autoregulatory failure can evolve mainly in the affected vascular territory. Treatment with rtPA does not separately affect the mechanism of cerebral autoregulation over a longer time period after thrombolysis. Blood pressure control strategies in large ischemic stroke should be guided by the status of vessel recanalization and autoregulatory capacity.

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