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Secondary decline of cerebral autoregulation is associated with worse outcome after intracerebral hemorrhage

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Abstract *Purpose:* Blood pressure management in acute intracerebral hemorrhage (ICH) relies on functioning cerebral autoregulation. The time course of autoregulation in acute ICH and its relation with clinical outcome are not known. *Methods:* Twenty-six patients with spontaneous ICH were studied on days 1, 3 and 5 after ictus. Autoregulation was noninvasively measured from spontaneous fluctuations of blood pressure and middle cerebral artery flow velocity (assessed by transcranial Doppler) using the correlation coefficient index Mx. From the same signals, non-invasive cerebral perfusion pressure was calculated. Results were compared with 55 healthy controls and related with clinical and radiological factors and 90-day outcome (modified Rankin scale). *Results:* Average Mx values of all patients did not differ across days or from controls. Higher Mx (i.e., poorer autoregulation) on day 5 was significantly related with lower Glasgow coma score, ventricular hemorrhage (both sides) and lower noninvasive cerebral perfusion pressure (ipsilateral). Increasing ipsilateral Mx between days 3 and 5 was related with lower Glasgow coma score and ventricular hemorrhage. In a multivariate analysis controlling for other hemodynamic factors, higher ipsilateral Mx on day 5 ($p = 0.013$) was a significant predictor for poor 90-day outcome.
Conclusions: Cerebral autoregulation is primarily preserved in acute ICH, but a secondary decline mainly ipsilateral to the ICH can occur. This is associated with poor clinical status, ventricular hemorrhage, lower cerebral perfusion pressure and worse clinical outcome.

Keywords Cerebral autoregulation · Spontaneous intracerebral hemorrhage · Transcranial Doppler sonography

Introduction

Spontaneous intracerebral hemorrhage (ICH) is one of the most severe complications of chronic hypertension, and its incidence can be dramatically reduced by antihypertensive treatment [1]. There is controversy about optimal treatment of ICH, including surgical versus non-surgical treatment [2], and blood pressure treatment is difficult

once ICH has happened. For example, high blood pressure may lead to secondary enlargement of the ICH because of hematoma growth, and early lowering of blood pressure may reduce this process [3]. Conversely, excessive lowering of blood pressure may cause hypoperfusion particularly in areas adjacent to the hemorrhage and thus worsen outcome [4].

A critical decrease of cerebral blood flow during lowering of cerebral perfusion pressure can be prevented by functioning cerebral autoregulation. Only a few previous clinical studies in ICH were performed applying the concept of static autoregulation [5] as an intrinsic brain-protective mechanism. In patients with ischemic stroke, the autoregulatory mechanism deteriorates over the first days, particularly in patients with poor outcome [6, 7]. It is not known whether such a phenomenon exists for ICH.

Noninvasive and easy to repeat assessment of cerebral autoregulation has become possible by recording the brain autoregulatory response to spontaneous blood pressure fluctuations with transcranial Doppler sonography [8, 9]. This rapid component of autoregulation may be even more vulnerable to acute brain damage than the slower static amplitude adjustments [10].

This study investigates whether cerebral autoregulatory failure occurs during the acute stage of ICH and how this associates with clinical outcome.

Subjects and methods

Patients and controls

We prospectively studied 29 patients admitted to the neurocritical care units of the Freiburg University Neurocenter with spontaneous ICH confirmed on computed tomography (CT) or magnetic resonance (MR) imaging. Exclusion criteria were significant internal carotid artery obstruction (≥70%) on either side as shown by ultrasound or MR/CT angiography and an insufficient bilateral temporal bone window for insonation of the middle cerebral artery (MCA). Written informed consent was obtained from patients or their relatives. The study was approved by the local ethics committee. Out of the 29 included patients, 3 were excluded because of another final etiology (hemorrhagic metastasis, $n = 1$) or inability to tolerate transcranial Doppler monitoring ($n = 2$).

Reference values of cerebral autoregulation (average of right and left MCA) were obtained from 55 age- and sex-matched subjects (64 ± 8 years, 44 men) randomly chosen from our previously studied control person pool. Twenty-five of these subjects had been measured twice within a period of 53 ± 32 days to assess the within-subject variability. None of the control persons had a history of cerebrovascular disease or any carotid artery obstruction on duplex ultrasound.

Clinical and neuroimaging data

All patients underwent routine neurocritical care including close monitoring of blood pressure, heart rate, temperature, blood glucose level and neurological status. Blood pressure management was based on current ICH management guidelines [4] and performed by treating physicians unaware of any autoregulation data. Four patients were sedated and ventilated. A ventricular drainage was placed in case of ventricular hemorrhage or if hydrocephalus evolved ($n = 8$); frameless stereotactic puncture and drainage were performed in case of a large hematoma ($n = 8$). Likewise, intraventricular or direct intraclot thrombolysis was performed with urokinase in case of large intraventricular hemorrhage or large hematoma ($n = 8$). All patients received routine medication, including antihypertensive agents, statins, glucose-lowering, antithrombotic and antibiotic medication. Various combinations of intravenous vasodilating medication (urapidil, dihydralazine, clonidine) were used in 30 of 78 measurements ($n = 9$ with dihydralazine, $n = 19$ with urapidile, $n = 7$ with clonidine). Sedation in ventilated patients was maintained using propofol (doses used 40–60 mg/h) or midazolam (4.8–19.2 mg/h) and fentanyl (0.025–0.05 mg/h). The 90-day outcome (modified Rankin Scale, mRS) was assessed via telephone interview with patients or their relatives by an examiner blinded to any autoregulation results [11].

The presence of intraventricular hemorrhage and the volume of ICH were estimated blinded to any autoregulation data from initial computed tomography or magnetic resonance images (performed at a mean of 8 ± 10 h after onset of symptoms) according to the ABC/2 rule for regularly shaped and ABC/3-rule for irregularly shaped hematomas (where ABC stands for length, width and depth of the hemorrhage in cm) [12]. Follow-up imaging on day 4 or 5 was only available in 10 of 26 patients and because of potential selection bias was not correlated with the course of autoregulation. Vascular risk factors (hypertension, diabetes, statin-treated hyperlipidemia, current smoking) were assessed according to patients' history review, previous medication and standard laboratory tests.

Hemodynamic measurements

Three measurements of autoregulation were performed: day 1 (12–24 h after ictus), day 3 (48–72 h) and day 5 (96–120 h). Cerebral blood flow velocity (CBFV) was assessed in both middle cerebral arteries with 2-MHz transducers by transcranial Doppler (DWL-Multidop-X©, Germany). Arterial blood pressure (ABP) was recorded continuously via a finger plethysmograph (Finapres©, Ohmeda, USA). End-tidal CO_2 partial pressure (P_{CO_2}) was measured in mmHg with an infrared capnometer

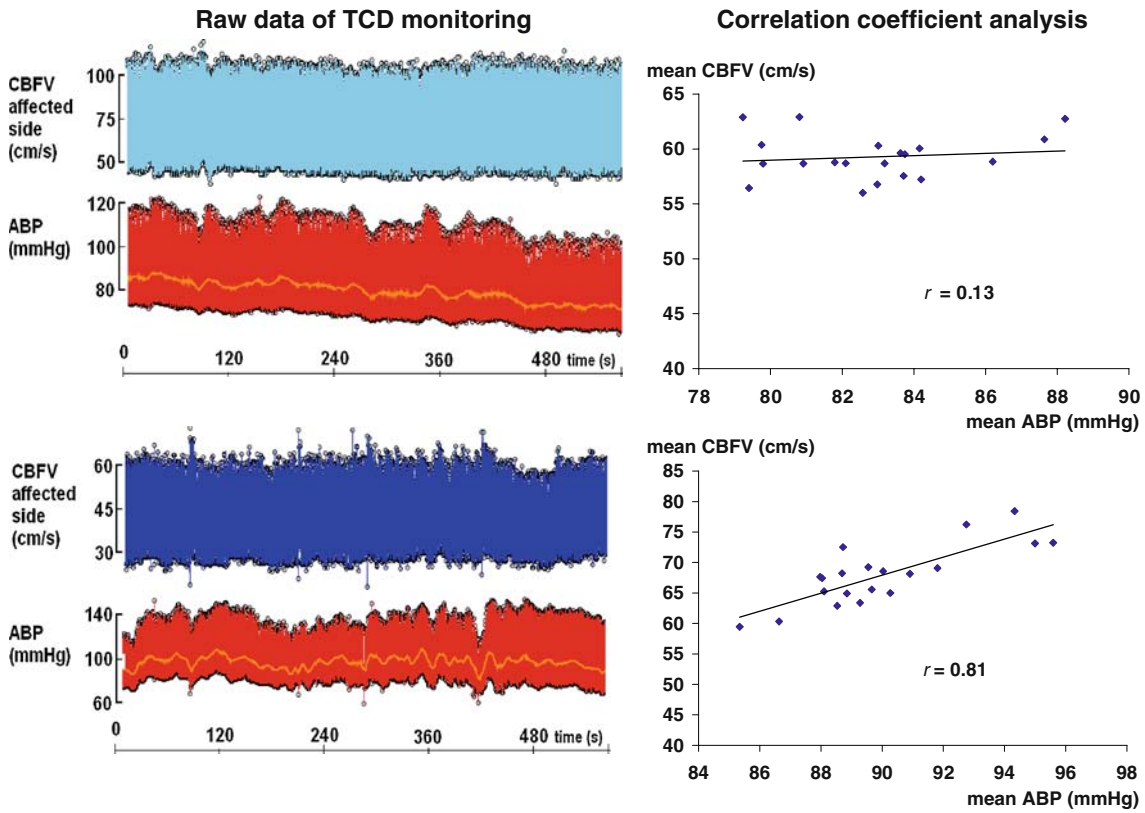

Fig. 1 Examples of autoregulation analysis. *Upper row*: Correlation plot of 20 segments of 3-s duration of mean ABP and CBFV. The index Mx is formed by averaging ten such correlation coefficients from a 10-min recording. The absent correlation means working autoregulation. *Lower row* shows positive correlation between ABP and CBFV indicating disturbed autoregulation

(Normocap Datex, Finland) during nasal expiration. After establishing stable hemodynamic values, a data segment of 8–10 min of spontaneous fluctuations was recorded. Intracranial pressure (nICP) was noninvasively estimated in all patients from the ABP and ipsilateral CBFV waveforms as described previously [13]. Mean noninvasive cerebral perfusion pressure (nCPP) was calculated as the difference between mean ABP and mean nICP during the measurement period. Glasgow Coma score (GCS) was assessed at each autoregulation study in patients not sedated and ventilated.

We applied the previously described correlation coefficient index method (index Mx) for grading of dynamic cerebral autoregulation [8, 14]. Hereby, mean values of ABP and CBFV were averaged over 3 s. From every 20 such segments (i.e., 60-s periods) separate Pearson's correlation coefficients between ABP and CBFV were calculated. The resulting 1-min correlation coefficients were then averaged to form the autoregulatory index Mx. This index was calculated for MCA sides ipsi- and contralateral to the ICH. Figure 1 shows an example of this analysis. A detailed description of Mx calculation is given in Online Resource 1.

Statistical analysis

Mixed effects models were used to assess the development of clinical and hemodynamic parameters across days. Explorative linear regression was used to assess the correlation of absolute Mx values (and changes of Mx between days) with the following independent factors: age, sex, history of hypertension, initial ICH volume, intraventricular hemorrhage on initial brain imaging, GCS, nCPP and endtidal P_{CO_2} at the time of each study. The Mx change between days was correlated with absolute GCS and nCPP values for both days. Separate analyses were performed for Mx values ipsi- and contralateral to the ICH. The effect of intravenous vasodilating medication on Mx values on both sides was tested with two-sample *t* tests. To compare the within-subject variability of Mx values, the modulus of Mx change (affected side) between days 3 and 5 was compared with that of the repeated measurements (right MCA) in healthy controls. Univariate linear regression was applied to assess how much of the variation of the clinical outcome (mRS at day 90) can be explained by the autoregulation parameter Mx and by other factors.

Table 1 Clinical characteristics

Characteristic	Value
Age (years)	65 ± 11
Sex male/female (*n*)	21/5
NIH Stroke Score on admission[a] (patients)	12 ± 7
Glasgow Coma Scale on admission[a] (patients)	13 ± 2
Modified Rankin scale at 90 days (patients)	3.3 ± 1.9
Mortality at 90 days [*n* (%)]	2 (8)
Side of hemorrhage, right/left (*n*)	17/9
Deep location [*n* (%)]	21 (81)
Lobar location [*n* (%)]	5 (19)
ICH volume (ml)	26 ± 22
Intraventricular hemorrhage [*n* (%)]	14 (54)
Hypertension [*n* (%)]	24 (92)
Diabetes mellitus [*n* (%)]	4 (15)
Smoking [*n* (%)]	9 (35)
Hyperlipidemia [*n* (%)]	6 (23)
Oral anticoagulation [*n* (%)]	5 (19)

ICH intracerebral hemorrhage, *NIH* National Institutes of Health
[a] Only assessed in non-intubated patients ($n = 22$). Values are mean ± standard deviation where appropriate

Multivariate linear regression analyses were then used to assess the association of Mx and clinical outcome (mRS at day 90) controlling for other cerebral hemodynamic data like CBFV in the MCA, nCPP as well as factors potentially influencing cerebral hemodynamics like age, sex, ICH volume and presence of ventricular hemorrhage.

Results

Clinical characteristics of the 26 studied patients are shown in Table 1. Most hemorrhages were located deep in the brain, and the main cause was hypertension ($n = 20$) or oral anticoagulation ($n = 5$); in one case the etiology could not be determined.

Autoregulation could not be assessed in 10 of the 78 overall scheduled studies. Reasons were Doppler or ABP signal artifacts ($n = 7$), patient death ($n = 2$) or patient referral to other hospitals ($n = 1$); only unilateral Doppler measurements were possible in two studies.

Cerebral autoregulation during acute ICH, clinical and hemodynamic parameters

Mean values of Mx differed neither significantly across study points nor when compared with healthy controls for ipsi- and contralateral sides (Table 2). The modulus of Mx change between days 3 and 5 on affected sides (0.19 ± 0.16) was higher than that of repeated measurements in controls (0.10 ± 0.11; $p = 0.021$). Mean endtidal P_{CO_2}, mean ABP, nICP and nCPP did not significantly differ among study points. Mean cerebral blood flow velocity increased significantly from day 1 to days 3 and 5 on both sides.

Table 2 Course of clinical status, hemodynamics and autoregulation

	Day 1	Day 3	Day 5
Time since onset of symptoms (h)	21 ± 9	61 ± 8	108 ± 7
Glasgow Coma Scale (patients)	12.1 ($n = 22$; SE = 0.69)	12.8 ($n = 23$; SE = 0.71; $p = 0.2687$)	12.5 ($n = 23$; SE = 0.76; $p = 0.1996$)
Mean MAP Finapres (mmHg)	90.9 ($n = 26$; SE = 4.26)	85.5 ($n = 21$; SE = 4.57; $p = 0.2220$)	84.4 ($n = 22$; SE = 4.51; $p = 0.1337$)
Mean MCA CBFV (cm/s)			
Ipsilateral	43.6 ($n = 26$; SE = 3.4)	55.8 ($n = 21$; SE = 3.6; $p = 0.0020$)	53.6 ($n = 22$; SE = 3.6; $p = 0.0091$)
Contralateral side	47.7 ($n = 26$; SE = 3.5)	56.6 ($n = 21$; SE = 3.7; $p = 0.0150$)	57.9 ($n = 22$; SE = 3.7; $p = 0.0051$)
Noninvasive ICP (mmHg)			
Ipsilateral	19.3 ($n = 25$; SE = 1.5)	18.7 ($n = 22$; SE = 1.6; $p = 0.7582$)	18.6 ($n = 21$; SE = 1.6; $p = 0.7356$)
Contralateral side	18.4 ($n = 24$; SE = 1.6)	19.3 ($n = 22$; SE = 1.7; $p = 0.6840$)	19.9 ($n = 21$; SE = 1.7; $p = 0.4636$)
P_{CO_2} endtidal (mmHg)	34.9 ($n = 26$; SE = 0.9)	34.3 ($n = 21$; SE = 0.98; $p = 0.5322$)	35.1 ($n = 22$; SE = 0.96; $p = 0.8815$)
Autoregulation index Mx			
Ipsilateral	0.24 ($n = 26$; SE = 0.04)	0.29 ($n = 21$; SE = 0.04; $p = 0.2650$)	0.21 ($n = 22$; SE = 0.04; $p = 0.5003$)
Contralateral side	0.27 ($n = 26$; SE = 0.04)	0.32 ($n = 21$; SE = 0.04; $p = 0.1912$)	0.22 ($n = 20$; SE = 0.04; $p = 0.2531$)

Development of parameters across study points. Mean values are given and in parenthesis the number of non-missing values, and from linear mixed effect models the standard error and the *p* value comparing the values at the follow-up study points (day 3, day 5) to the baseline study point (day 1). There were no significant differences between ipsi- and contralateral sides on any day. Mx values in 55 controls averaged 0.27 (SE = 0.02). Mx on ipsi- and contralateral sides in patients did not significantly differ from these values on any day. GCS was only assessed in patients without intubation and sedation

Univariate factors associated with cerebral autoregulation

On day 5, higher Mx (poorer autoregulation) was related with lower GCS (ipsilateral $p < 0.001$, contralateral $p = 0.006$), the presence of ventricular hemorrhage (ipsilateral $p = 0.011$, contralateral $p = 0.018$) and to lower nCPP (ipsilateral $p = 0.024$). Lower Mx was related with higher age on day 1 ($p = 0.013$ for both sides), but not on other days. Increasing ipsilateral Mx (worsening autoregulation) between days 3 and 5 was related with lower GCS on day 5 ($p = 0.014$) and with the presence of ventricular hemorrhage ($p = 0.0486$). There were no significant differences in Mx values between measurements with and without intravenous vasodilating medication.

Course of cerebral autoregulation and clinical outcome

Considering the individual time course, for most patients ipsilateral Mx changed only slightly between days 1 and 3, but drastically between days 3 and 5. Individual figures of the course of ipsilateral Mx suggest that there are two groups of patients with different outcomes: increasing Mx between days 3 and 5 (worsening autoregulation) with poor clinical outcome and decreasing Mx between days 3 and 5 (improving autoregulation) with better clinical outcome (Fig. 2).

Univariate analysis showed that GCS and the presence of ventricular hemorrhage were the most important classical predictors of clinical outcome, and that ipsilateral Mx on day 5 and the change of ipsilateral Mx between days 3 and 5 were potential predictors for clinical outcome (Table 3). In a multivariate analysis, ipsilateral Mx remained a significant independent predictor for clinical outcome (Table 4).

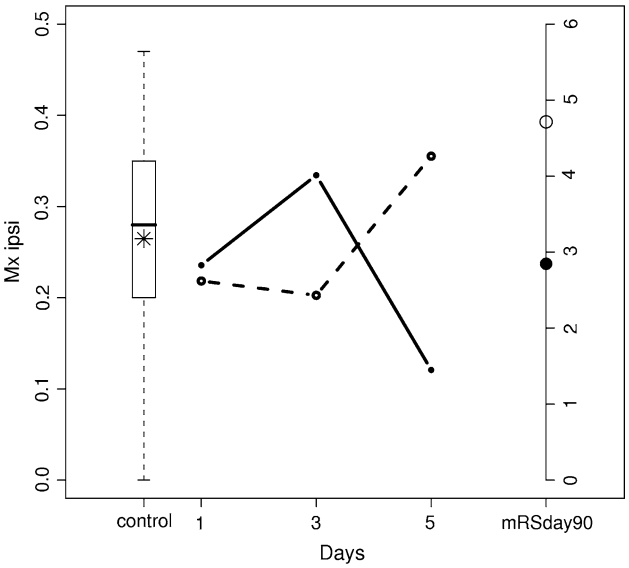

Fig. 2 Course of cerebral autoregulation in acute ICH and outome. Mean development of ipsilateral Mx and the mean clinical outcome (mRS at day 90) separated for two groups of patients: the one where Mx is decreasing ($n = 13$) between days 3 and 5 is given by a solid line and filled points, the other where Mx is increasing ($n = 7$) between days 3 and 5 by a dashed line and empty points. The plot presents only these patients ($n = 20$) in whom all three measurements were available. The *boxplot* shows the Mx values of the control group of healthy subjects ($n = 55$); the *asterisk* denotes the mean value

Table 3 Univariate analysis for clinical outcome (mRS day 90)

Factor	Coef	*p* Value	Adj. R^2
GCS day 1	−0.50	0.000009	0.66
Mx ipsilateral difference day 3–5	7.25	0.000049	0.59
Mx ipsilateral day 5	6.78	0.00017	0.49
GCS day 5	−0.37	0.000395	0.47
Ventricular hemorrhage	2.27	0.00108	0.34
GCS day 3	−0.34	0.00455	0.33
GCS on admission	−0.37	0.032527	0.17
Mx contralateral day 5	4.78	0.0431	0.16
ICH volume	0.04	0.04086	0.13

No significant effects were found for age, sex, autoregulation values at days 1 and 3, mean ABP, nCPP or nICP at any study
nCPP noninvasive cerebral perfusion pressure, *nICP* noninvasive intracranial pressure

Discussion

This preliminary clinical study confirmed that cerebral autoregulation is not disturbed generally and early in acute ICH [5]. However, in some patients later decline of individual autoregulatory ability can occur, and the outcome is significantly worse in this case.

The reason of deteriorating autoregulation during the acute stage of ICH is not that obvious because of the small number of cases included in the study. Poorer or worsening autoregulation on affected sides was related with lower nCPP. A focal mass effect may decrease hemispheric cerebral perfusion pressure and thereby disturb ipsilateral dynamic autoregulation in the affected hemisphere between days 3 and 5. Poorer autoregulation was also related with intraventricular hemorrhage. The causality of this association cannot be determined from the present data. One explanation is that intraventricular hemorrhage could have led to concomitant hydrocephalus and reductions in individual CPP.

However, a direct failure of the autoregulation mechanism during acute ICH may also occur. In acute ischemic stroke, secondary dynamic and static autoregulatory failure has been described [6, 14]. This is partly caused by a vicious circle induced by reperfusion leading

Table 4 Multivariate analysis for clinical outcome (mRS day 90)

Factor	Estimate	Standard error	*p* Value
Mx			
Model 1 (Mx ipsilateral day 5), adj. $R^2 = 0.50$			
Mx ipsilateral day 5	5.889	1.966	0.013
nCPP ipsilateral day 5	0.027	0.02	0.204
Mean CBFV ipsilateral day 5	0.007	0.018	0.703
ICH volume	0.013	0.017	0.454
Ventricular hemorrhage	0.757	0.712	0.307
Age	0.03	0.026	0.272
Male sex	−0.952	0.919	0.319
Model 2 (Mx ipsilateral difference day 3–5), adj. $R^2 = 0.48$			
Mx ipsilateral difference day 3–5	6.826	2.205	0.01
Mx ipsilateral day 3	4.927	2.439	0.068
nCPP ipsilateral day 5	0.016	0.022	0.476
Mean CBFV ipsilateral day 5	−0.008	0.021	0.709
ICH volume	0.016	0.018	0.394
Ventricular hemorrhage	0.503	0.737	0.509
Age	0.016	0.029	0.597
Male sex	−0.289	1.053	0.789

The Mx model using the difference between days 3 and 5 was additionally corrected for absolute values on day 3

nCPP noninvasive cerebral perfusion pressure, *ICH* intracerebral hemorrhage

to increased local production of reactive oxygen species damaging arteriolar smooth muscles as the main effectors of autoregulation [15]. Other causes are spreading local acidosis and edema [6]. In acute ICH, both reactive oxygen species (as a result of inflammatory mechanisms by acute brain injury [16]) and local acidosis and edema are present. Such direct damage of the autoregulatory mechanism may be part of the pathophysiology of ICH.

We found that poorer autoregulation on day 5 was a predictor of poor clinical outcome independent from other hemodynamic variables or factors potentially influencing cerebral hemodynamics (Table 4). This association does not prove any causal relationship. It may be a result of greater brain damage by subsequent episodes of hypo- or hyperperfusion because of direct autoregulatory failure. Conversely, both worsening autoregulation and bad outcome could be the common result of a more severe mass effect and brain injury affecting perfusion pressure, cerebral vessels and autonomic pathways.

Transcranial Doppler sonography only allows assessment of hemodynamics in the whole MCA territory, which predominantly reflects cortical arterioles. Isolated deep perifocal autoregulatory failure in individual patients thus cannot be detected by the present study; the emphasis rather lies on the functionally important cortico-subcortical areas. The increase of absolute mean cerebral blood flow velocity on both sides during the acute stage of ICH may be explained by routine intravenous fluid substitution leading to moderate reduction of hematocrit values [17].

The applied autoregulation index Mx has been well validated against static measurements of autoregulation [18] and correlated with the classical threshold of autoregulation [19]. At present, it has the best evidence for noninvasive autoregulation monitoring in neurocritical care patients [20]. As a limitation, Mx was determined noninvasively using ABP instead of CPP. Still, noninvasive Mx shows acceptable correlation with invasively determined Mx, and both approaches are able to indicate poor outcome in traumatic brain injury [21]. Using short source data segments of few seconds length, Mx reflects primarily dynamic properties of autoregulation. Of importance, Mx is a continuous index of autoregulation, and any absolute thresholds should be applied with caution. Our results show that in ICH patients absolute Mx values still within the upper range of control persons (Fig. 2) may already indicate an inferior state of autoregulation because of their clear association with poorer clinical state and outcome. These values evolved by changes from an individual "normal" Mx level and are likely to indicate individual deterioration of autoregulation (i.e., Mx change between days 3 and 5). Still, one cannot fully rule out that the present variation of Mx is a random effect. The present changes in Mx between days 3 and 5 were, however, larger than those of repeated measurements in the control group assessed over an even longer time span. It has been previously shown that the individual time course of Mx values may have a greater diagnostic potential than independent absolute values in critically ill patients [22].

This is an observational clinical study limited by the needs of routine patient care and its small sample size. There are possible interactions with intravenous vasoactive medications, in particular dihydralazine. A significant effect of these medications on Mx values could not be found. However, because of the small sample size this does not preclude any influence of vasodilators on autoregulation. Furthermore, statin treatment may improve autoregulation and outcome in acute subarachnoid hemorrhage [23]. Only three of the present patients were treated with statins, preventing any meaningful analysis. The impact of short-term statin treatment on dysautoregulation in individual ICH patients may be of future interest, although outcome in patients pre-treated with statins was not generally better in observational studies [24]. Regarding the applied transcranial Doppler methodology, the presence of a mass lesion could have led to physical distortion of the insonated MCA. In this situation, the CBFV signal in the MCA still reflects downstream arteriolar resistance. Strong distortion should have led to compression or kinking of the MCA, leading to a stenotic signal with clearly elevated, turbulent CBFV. This was, however, not observed in the present patients. Finally, the present mode of nCPP calculation from noninvasive signals is limited by the possibility of covariance because the same fingerplethysmographic ABP signal was used to calculate nICP and nCPP. Results of nCPP should thus be regarded with caution.

Previous clinical studies challenged the lower threshold of static autoregulation in acute ICH by

pharmacological ABP reduction [5, 25–27]. Only one study assessed the time course of autoregulation in deep ICH [27]. Three days after ICH, autoregulation in both hemispheres was globally impaired mainly with MAP reduction of more than 20%. Impairment was less pronounced around the clot because of possible false autoregulation. Three weeks after ICH, poor periclot autoregulation with restored autoregulation in the hemispheres was observed. Powers et al. [5] found no negative influence of reducing mean ABP up to 15% on early periclot or global blood flow during the first 24 h.

Two studies measured cerebral vasoreactivity in acute ICH. A Doppler study found CO_2 reactivity to hypocapnia (vasoconstrictory response) measured within 48 h dependent on ICP and related with clinical outcome [28]. A recent study continuously monitored the correlation between ABP and ICP in critically ill ICH patients [29]. The calculated pressure reactivity index indirectly reflects autoregulatory activity. Impaired mean values averaged over the whole monitoring period of days 2–5 after onset of ICH were related with poor clinical status at discharge and lower CPP.

As in previous studies, most of our patients had chronic hypertension, which may additionally impair autoregulation [30]. There was no early relation of the presently observed nCPP or blood pressure ranges to Mx autoregulatory capacity. Yet, on day 5 lower nCPP related with poorer autoregulation on ipsilateral sides. This delayed dependency on perfusion pressure supports the hypothesis of secondary autoregulatory decline during acute ICH. Continuous monitoring studies in traumatic brain injury have emphasized the need for an "optimal" CPP adapted to the current autoregulatory status, regarding both lower and upper limits of CPP [31]. This may also hold true for ICH patients [29].

In conclusion, this pilot clinical study suggests that there is no general failure of autoregulation in acute ICH. In individual patients, however, secondary decline of cerebral autoregulation can evolve mainly in affected hemispheres. This is associated with poor clinical status, ventricular hemorrhage, lower cerebral perfusion pressure and worse clinical outcome.

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Conflict of interest statement There are no conflicts of interest.

References:

1. Steiner T, Kaste M, Forsting M, Mendelow D, Kwiecinski H, Szikora I, Juvela S, Marchel A, Chapot R, Cognard C, Unterberg A, Hacke W (2006) Recommendations for the management of intracranial haemorrhage–part I: spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee. Cerebrovasc Dis 22:294–316
2. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, Karimi A, Shaw MD, Barer DH (2005) Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet 365:387–397
3. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, Heeley E, Skulina C, Parsons MW, Kim JS, Tao QL, Li YC, Jiang JD, Tai LW, Zhang JL, Xu E, Cheng Y, Heritier S, Morgenstern LB, Chalmers J (2008) Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol 7:391–399
4. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, Mayberg M, Morgenstern L, Ogilvy CS, Vespa P, Zuccarello M (2007) Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Stroke 38:2001–2023
5. Powers WJ, Zazulia AR, Videen TO, Adams RE, Yundt KD, Aiyagari V, Grubb RL Jr, Diringer MN (2001) Autoregulation of cerebral blood flow surrounding acute (6 to 22 hours) intracerebral hemorrhage. Neurology 57:18–24
6. Dohmen C, Bosche B, Graf R, Reithmeier T, Ernestus RI, Brinker G, Sobesky J, Heiss WD (2007) Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. Stroke 38:56–61
7. Reinhard M, Wihler C, Roth M, Harloff A, Niesen WD, Timmer J, Weiller C, Hetzel A (2008) Cerebral autoregulation dynamics in acute ischemic stroke after rtPA thrombolysis. Cerebrovasc Dis 26:147–155
8. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD (1996) Monitoring of cerebral autoregulation in head-injured patients. Stroke 27:1829–1834
9. Christ M, Noack F, Schroeder T, Hagmueller A, Koch R, May SA, Morgenstern U, Ragaller M, Steinmeier R (2007) Continuous cerebral autoregulation monitoring by improved cross-correlation analysis: comparison with the cuff deflation test. Intensive Care Med 33:246–254
10. Dawson SL, Blake MJ, Panerai RB, Potter JF (2000) Dynamic but not static cerebral autoregulation is impaired in acute ischaemic stroke. Cerebrovasc Dis 10:126–132
11. Merino JG, Lattimore SU, Warach S (2005) Telephone assessment of stroke outcome is reliable. Stroke 36:232–233

12. Huttner HB, Steiner T, Hartmann M, Kohrmann M, Juettler E, Mueller S, Wikner J, Meyding-Lamade U, Schramm P, Schwab S, Schellinger PD (2006) Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. Stroke 37:404–408
13. Schmidt B, Czosnyka M, Raabe A, Yahya H, Schwarze JJ, Sackerer D, Sander D, Klingelhofer J (2003) Adaptive noninvasive assessment of intracranial pressure and cerebral autoregulation. Stroke 34:84–89
14. Reinhard M, Roth M, Guschlbauer B, Harloff A, Timmer J, Czosnyka M, Hetzel A (2005) Dynamic cerebral autoregulation in acute ischemic stroke assessed from spontaneous blood pressure fluctuations. Stroke 36:1684–1689
15. Cipolla MJ, Curry AB (2002) Middle cerebral artery function after stroke: the threshold duration of reperfusion for myogenic activity. Stroke 33:2094–2099
16. Wang J, Dore S (2007) Inflammation after intracerebral hemorrhage. J Cereb Blood Flow Metab 27:894–908
17. Bruder N, Cohen B, Pellissier D, Francois G (1998) The effect of hemodilution on cerebral blood flow velocity in anesthetized patients. Anesth Analg 86:320–324
18. Lang EW, Mehdorn HM, Dorsch NW, Czosnyka M (2002) Continuous monitoring of cerebrovascular autoregulation: a validation study. J Neurol Neurosurg Psychiatry 72:583–586
19. Brady KM, Lee JK, Kibler KK, Easley RB, Koehler RC, Shaffner DH (2008) Continuous measurement of autoregulation by spontaneous fluctuations in cerebral perfusion pressure: comparison of 3 methods. Stroke 39:2531–2537
20. Andrews PJ, Citerio G, Longhi L, Polderman K, Sahuquillo J, Vajkoczy P (2008) NICEM consensus on neurological monitoring in acute neurological disease. Intensive Care Med 34:1362–1370
21. Lang EW, Lagopoulos J, Griffith J, Yip K, Mudaliar Y, Mehdorn HM, Dorsch NW (2003) Noninvasive cerebrovascular autoregulation assessment in traumatic brain injury: validation and utility. J Neurotrauma 20:69–75
22. Soehle M, Czosnyka M, Pickard JD, Kirkpatrick PJ (2004) Continuous assessment of cerebral autoregulation in subarachnoid hemorrhage. Anesth Analg 98:1133–1139
23. Tseng MY, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ (2005) Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: a phase II randomized placebo-controlled trial. Stroke 36:1627–1632
24. FitzMaurice E, Wendell L, Snider R, Schwab K, Chanderraj R, Kinnecom C, Nandigam K, Rost NS, Viswanathan A, Rosand J, Greenberg SM, Smith EE (2008) Effect of statins on intracerebral hemorrhage outcome and recurrence. Stroke 39:2151–2154
25. Kaneko T, Sawada T, Niimi T, Naritomi H, Kuriyama Y, Kinugawa H (1983) Lower limit of blood pressure in treatment of acute hypertensive intracranial hemorrhage (AHCH). J Cereb Blood Flow Metab 5(Suppl 1):S51–S52
26. von Helden A, Schneider GH, Unterberg A, Lanksch WR (1993) Monitoring of jugular venous oxygen saturation in comatose patients with subarachnoid haemorrhage and intracerebral haematomas. Acta Neurochir Suppl (Wien) 59:102–106
27. Kuwata N, Kuroda K, Funayama M, Sato N, Kubo N, Ogawa A (1995) Dysautoregulation in patients with hypertensive intracerebral hemorrhage. A SPECT study. Neurosurg Rev 18:237–245
28. Klingelhofer J, Sander D (1992) Doppler CO2 test as an indicator of cerebral vasoreactivity and prognosis in severe intracranial hemorrhages. Stroke 23:962–966
29. Diedler J, Sykora M, Rupp A, Poli S, Karpel-Massler G, Sakowitz O, Steiner T (2009) Impaired cerebral vasomotor activity in spontaneous intracerebral hemorrhage. Stroke 40:815–819
30. Strandgaard S (1976) Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. Circulation 53:720–727
31. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, Pickard JD (2002) Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med 30:733–738