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Clinical Investigative Study

Computed Tomography and Transcranial Doppler Findings in Acute and Subacute Phases of Intracerebral Hemorrhagic Stroke

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ABSTRACT

BACKGROUND AND PURPOSE

The hematoma volume is an important determinant of outcome and a predictor of clinical deterioration in patients with intracerebral hemorrhage (ICH). Our goal was to evaluate alterations in the cerebral circulation, in respect to hemorrhage and edema volume changes, using transcranial Doppler (TCD).

METHODS

Twenty patients with acute supratentorial ICH were examined. Brain, hematoma, and edema volumes were calculated from CT scans performed at admission and 2 weeks later. Data were compared with those obtained from bilateral TCD recordings of the middle cerebral arteries.

RESULTS

During TCD examination, blood flow velocities did not change, cerebral perfusion pressure (CPP) and resistance area product (RAP) decreased ($P = .006$, $P = .002$) while cerebral blood flow index (CBFI) remained constant on the affected side. Although hemorrhage volume did not correlate with RAP in the acute phase, correlation was found in the subacute phase ($r = .44$, $P = .04$).

CONCLUSIONS

TCD monitoring sensitively demonstrates the hemodynamic change caused by ICH but the severity of the changes does not correlate with the volume of the ICH in acute stage. The CPP, RAP, and CBFI values are more sensitive parameters than the absolute velocity values, therefore they contribute more to the understanding of hemodynamic changes developed after spontaneous ICH.

Keywords: Cerebral hemodynamics, intracerebral hemorrhage, computed tomography, transcranial ultrasound.

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Introduction

Stroke is the third leading cause of death, responsible for ~5.7 million deaths each year, and the most frequent cause of long standing disability in the industrialized countries.[1,2] The prevalence of stroke and its relating cost undoubtedly rises as the aging population increases.[3] Similarly, the incidence of stroke markedly increases with age as well, contributing to the total morbidity and mortality.[4]

Although intracranial hemorrhage (ICH) accounts for only 10-30% of all stroke-related hospitalizations, it is one of the major causes of stroke-related death and disability. Overall mortality approaches 50% at 30 days, and approximately half of all ICH-related mortality occurs within the first 24 hours after the initial hemorrhage.[5] The explanation for this high mortality rate is yet unknown, however, circulatory changes and edema formation around the hemorrhage are suggested contributors. Edema development after ICH may elevate intracranial pressure (ICP) and cause brain herniation, brainstem compression, and death.[6] Clinical studies demonstrated that the peak of hemorrhage-induced deaths occurs within the first few days, and is likely to be associated with progressive edema development.[5,7] Numerous studies in animal models have defined the key role of the coagulation cascade and thrombin itself in the edema development during the first 24 hours, together with plasma protein extravasation, which oncotically induces rapid edema formation already at 1 hour after spontaneous ICH.[8–11] The coagulation cascade is activated as soon as blood encounters tissue. Perihematomal brain edema develops in response to clot retraction, thrombin formation, erythrocyte lysis, hemoglobin toxicity, complement activation, mass effect, and blood-brain barrier disruption.[12]

To our current knowledge, changes in the cerebral circulation after ICH are poorly understood due to a lack of information and follow-up measurements. There are only a few reports

comparing the results of transcranial Doppler (TCD) and CT findings in patients suffering from ICH. Furthermore, we did not find any previous data about the correlation between cerebral hemodynamical parameters (measured by TCD) and CT findings in acute and subacute stages of ICH. Since ICH has a great extent of therapeutic and prognostic uncertainty, any data about the correlation between ICH, developing edema, and intracranial hemodynamic parameters would be of great importance.

As for ICH detection, CT is still the gold standard diagnostic tool, as it allows the accurate distinction between hemorrhagic and ischemic stroke subtypes.[13] Traditionally, the noncontrast CT scan has been believed of as the mainstay and first-line imaging modality for ICH, also offering the ability to generate 3-dimensional volume estimates of blood accumulation.[14,15]

For collecting functional data of intracerebral circulation, TCD is an ideal, noninvasive, real-time bedside tool for evaluating cerebral vessels.[16,17] It has been extensively used in various clinical situations, while in the last two decades its role has been established in microemboli monitoring, intraoperative and intensive care monitoring, and in the management of patients with cerebrovascular disease and stroke as well.[18–26] In a recent publication, it was stated that TCD may assist in predicting hematoma growth, global ICP increase and prognosis. In particular, a pulsatility index (PI) increase in the contralateral hemisphere seemed to correlate with poor outcome.[27]

When designing this study, we were motivated by the idea, that the combination of the above two imaging techniques (cerebral CT and TCD) may provide new information about the relationship between functional parameters and ICH. In the light of all these, our aim was: (1) to assess the cerebral hemodynamics during the acute and subacute phases of spontaneous ICH, (2) to investigate the correlation between cerebral hemodynamic parameters and ICH (+ edema) volume, and (3) to analyze hypothetical differences between findings of the acute and subacute phases.

Materials and Methods

Patients

Patients with CT-documented ICH admitted to the Neurointensive Care Unit of the Department of Neurology, University of Debrecen between September 2000 and March 2002, were assessed for enrollment into the study. Eligibility was based on supratentorial ICH and CT scan within 12 hours after onset of any neurological deficit. Those patients who; (1) underwent surgical hematoma evacuation or ventriculostomy; (2) suffered traumatic hemorrhage, had cerebral neoplasm, aneurysm rupture, arteriovenous malformation, or coagulopathy; or (3) had inadequate temporal bone window for TCD examination, were excluded from the study. On the basis of these criteria, 35 patients were examined. Out of these patients, 15 died before the second examination, leaving a study population of 20 patients. General information concerning the participants and the site of the hemorrhages are given in Table 1.

The study protocol was reviewed and approved by the local ethics committee.

Table 1. Clinical Data of the Patients

Age (years)	59.5 (13)
Gender (F/M)	6/14
SNSS score at admission (Median and quartile ranges)	28.5 (26.5)
SNSS score at 2 weeks (Median and quartile ranges)	45 (25)
MAP at admission (mmHg)	121.1 ± 20.7
MAP at 2 weeks (mmHg)	99.9 ± 9.1
Hemorrhage location	
–Lobar	3
–Thalamic	6
–Subinsular	5
–Basal ganglia	6

SNSS = Scandinavian Neurological Stroke Scale.

Cerebral CT Scan

Scanning of patients was performed with Somatom DR CT scanner (Siemens, Erlangen, Germany). Brain, intracerebral hemorrhage, and edema volumes were calculated off-line from two series of CT scans performed during admission and 2 weeks (13.8 ± .7 days) after. Optical density readings were made using the Osiris version 3.6 software (OSIRIS Medical Imaging Software, Digital Imaging Unit, University Hospital of Geneva, Geneva, Switzerland). Lesion areas on each slice were calculated by tracing the perimeter of the appropriate high- or low-attenuation zone on the CT console; these values were then multiplied by slice thickness (4 mm) to yield single-plane lesion volumes, which were summed up to yield total lesion volume.

TCD Monitoring

TCD examination was performed within 2-3 hours after the first and follow-up CT scans with a 2 MHz probe of the Multi-Dop T2 (DWL Electronische Systeme GmbH, Sipplingen, Germany) TCD device. The TCD investigator was aware of the fact that the patients were suffering from a hemorrhagic stroke, but was unaware of the size and exact location of the bleeding.

The middle cerebral artery (MCA) was insonated bilaterally at 50 mm depth through the temporal bone window using a handheld probe. The same sample volume (10 mm), power (100 mW), gain (20%), and filter (50 Hz) parameters were used in both examinations. Patients were examined in supine position. Mean, systolic, diastolic flow velocities (FV) and PI were recorded bilaterally in the MCA. PI was calculated according to the formula of Gosling as follows: PI = (Systolic FV-Diastolic FV)/Mean FV.[28]

We calculated the following hemodynamic parameters as well according to Aaslid et al: estimated cerebral perfusion pressure (ECPP) = [Vmean/(Vmean – Vdiast)] × (BPmean – BPdiast), resistance area product (RAP) = BPmean/Vmean and cerebral blood flow index (CBFI) = ECPP/RAP. Vmean and Vdiast are the mean and diastolic blood FV, respectively in the MCA. BPmean and BPdiast are the mean and diastolic blood pressures, respectively.[29]

These calculations were performed because we intended to take into account mean arterial pressure (MAP)

Table 2. Comparison of Brain, Hemorrhage, and Edema Volumes during the First and Second Investigations (Median and Quartile Ranges)

Volume (cm^3)	1st	2nd	*P* Value
Brain	1,100 (201.15)	1,154 (174.2)	.295
Hemorrhage	6.84 (15.17)	4.01 (6.71)	<.0001
Edema	10.45 (15.79)	20.55 (20.63)	<.0001
Hemorrhage + Edema	16.68 (30.96)	24.89 (26.32)	.0015

changes between the two examinations. Both the CPP and the RAP were derived from the systemic blood pressure while the CBFI, which reflects cerebral blood flow in the MCA territory, depended on the CPP and RAP changes.[29–31] Blood pressure was measured on the right arm by a standard mercury sphygmomanometer, just before the TCD measurements.

Clinical Evaluation

Clinical status of the patients was evaluated on the first day of hospitalization and 2 weeks later. The severity of symptoms was evaluated using the Scandinavian Neurological Stroke Scale (SNSS).[32] The scale had prognostic items with a maximal score of 22, and long-term items as well, with a maximal score of 48. Routine laboratory results (blood counts, hemostasis parameters, electrolytes, lipids, etc.) were collected during admission.

Statistical Analysis

Statistica for Windows version 5.5 (StatSoft, Tulsa) was used for data analysis. Volumes (hemorrhage, edema) and SNSS scores did not have a normal distribution, therefore median and quartile ranges were given. Flow parameters were presented as means (SD). For any comparison where volume was involved, nonparametric statistics was used. Normality of variables was checked by the Shapiro-Wilk test. For paired comparisons, the appropriate paired *t*-test or the Wilcoxon matched pairs test were used. The Spearman rank order correlation was used to describe relationship between variables with not normal distribution. Statistical significance was assumed if $P < .05$.

Results

The clinical status of our patients improved significantly as expected by the improved SNSS scores (29.3 ± 14.8, 44.1 ± 14.1 at admission and at 2 weeks, respectively, $P < .0001$).

Volumetric Measurements

Brain, hemorrhage, surrounding edema, and hemorrhage + edema volumes are shown in Table 2. The brain volume did not change significantly after 2 weeks. The hemorrhage volume significantly decreased ($P < .0001$), while edema and hemorrhage + edema volumes increased ($P < .0001$ and $P = .0015$, respectively) between the two examinations. Hemorrhage volume correlated with the SNSS scores at the first examination ($r = -.68$, $P = .0008$) as shown in Figure 1, indicating that the larger the hemorrhage, the lower the SNSS score. During the second examination, a weaker, but still significant correlation could be found between hemorrhage volume and SNSS scores ($r = -.46$, $P = .04$).

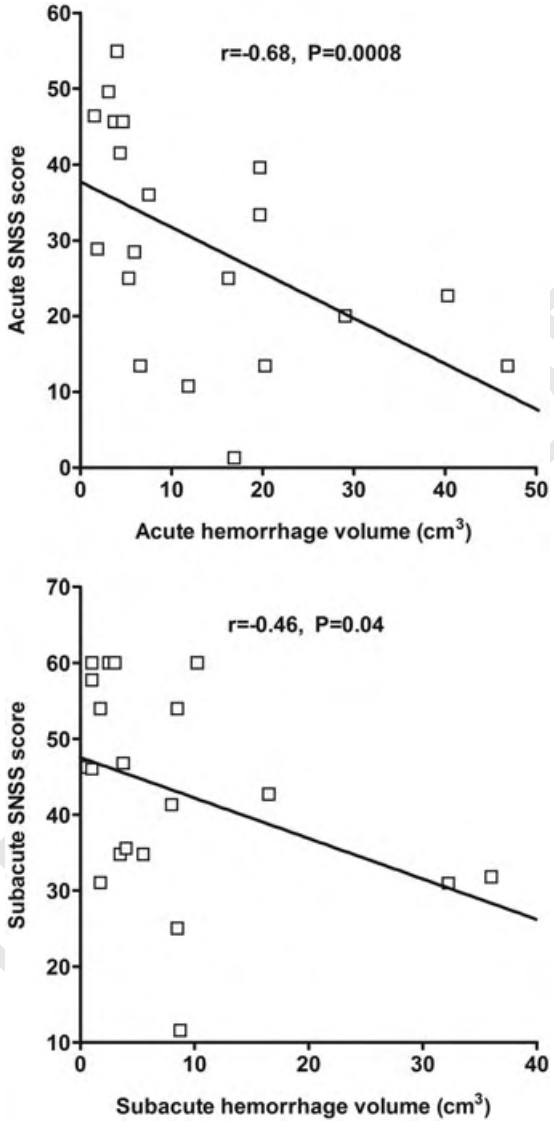

Fig 1. Correlations between hemorrhage volume and Scandinavian Neurological Stroke Score in the acute and subacute phases of ICH.

TCD Measurements

All TCD parameters (mean, systolic, diastolic blood FV) were significantly less on the hemorrhagic side ($P = .008$, $P = .015$, and $P = .013$, respectively) compared to those on the contralateral side, except PI, the index of peripheral vascular resistance ($P = .08$). At the 2-week follow-up (subacute phase of ICH), these differences remained still significant, along with PI becoming also significantly higher compared to the contralateral side ($P = .01$, $P = .046$, $P = .008$, and $P = .024$, respectively) (Table 3). During the 2-week period the volume of ICH decreased significantly, the clinical status improved (SNSS scores: $P < .0001$) without any improvement of ipsilateral velocities and PI. The differences between the ipsi- and contralateral side remained significant.

As there were no significant changes in measured TCD parameters, but there was an approximately 17.5% decrease of

Table 3. Cerebral Blood Flow Velocities (cm/s) of the Affected and Nonaffected Sides during the First and Second Examinations (Mean ± SD)

	Affected Side	Nonaffected Side	*P* Value
First Examination			
FVmean (cm/s)	32.45 ± 8.07	39.15 ± 12.57	.0079
FVsys (cm/s)	59 ± 13.15	68.5 ± 17.46	.0158
FVdiast (cm/s)	19.5 ± 6.52	24.4 ± 10.69	.0129
PI	1.24 ± .26	1.18 ± .27	.0789
Second Examination			
FVmean (cm/s)	35.2 ± 10.74	41.2 ± 14.39	.0106
FVsys (cm/s)	64.1 ± 19.13	71.6 ± 21.44	.0467
FVdiast (cm/s)	21.1 ± 7.83	26 ± 11.48	.0086
PI	1.26 ± .27	1.15 ± .22	.024

FVmean = mean cerebral blood flow velocity; FVsys = systolic cerebral blood flow velocity; FVdiast = diastolic cerebral blood flow velocity; PI = pulsatility index.

Table 4. Comparison of the Cerebral Perfusion Pressure, Resistance Area Product, and Cerebral Blood Flow Index during the First and Second Examinations

	First Examination	Second Examination	*P* Value
Affected Side			
CPP (mmHg)	65.87 ± 21.85	50.54 ± 12.31	.006
RAP (mmHg/(cm/s))	3.99 ± 1.34	3.09 ± .99	.002
CBFI (cm/s)	17.7 ± 6.65	17.94 ± 7.46	.912
Nonaffected Side			
CPP (mmHg)	68.01 ± 22.09	53.25 ± 12.41	.012
RAP (mmHg/(cm/s))	3.34 ± 1.03	2.69 ± .94	.005
CBFI (cm/s)	22.33 ± 9.83	22.75 ± 12.23	.877

CPP = cerebral perfusion pressure; RAP = resistance area product; CBFI = cerebral blood flow index.

MAP between the two examinations, CPP, RAP, and CBFI values were derived from MAP and FV values. After 2 weeks, CPP and RAP decreased significantly on the affected side ($P = .006$ and $P = .002$, respectively), while CBFI remained constant ($P = .912$). In the nonaffected side CPP and RAP also decreased significantly ($P = .012$, $P = .005$, respectively), while CBFI remained constant ($P = .877$) between the two examinations (Table 4). During the acute phase, CPP was similar on both sides, while RAP was higher ($P = .011$) and CBFI was lower ($P = .016$) on the affected than the nonaffected side. Similarly to the first examination, in the subacute phase, CPP was the same on both sides, while RAP was higher ($P = .014$) and CBFI was lower ($P = .009$) on the affected side.

Relationship between FVs and Volumetric Measurements

We did not find any correlation between the FV, PIs and hemorrhage, edema or hemorrhage + edema volumes in any of the two examinations. Figure 2 depicts the relationship between ICH volume and ipsilateral/contralateral PI ratio. During the acute phase, the ipsilateral/contralateral PI ratio did not correlate with the hematoma volume ($r = .4$, $P = .1$), while at the second examination hemorrhage volumes correlated strongly with ipsilateral/contralateral PI ratios ($r = .56$, $P = .009$).

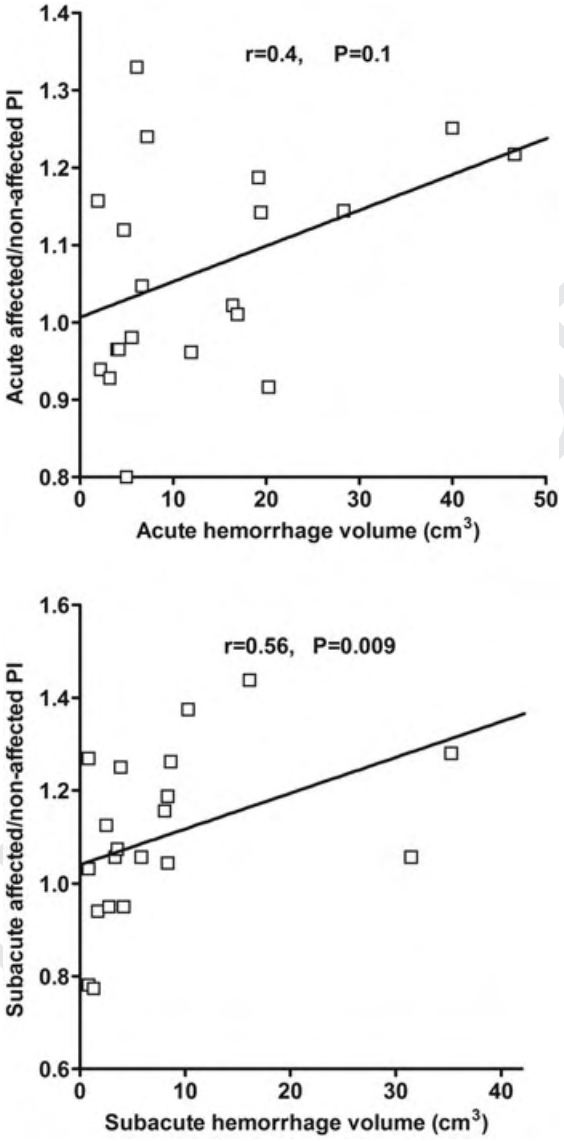

Fig 2. Correlations between hemorrhage volume and affected/nonaffected PI ratios in the acute and subacute phases of ICH.

Relationship between Hemorrhage Volume and RAP, during the Acute and Subacute Phases

In the acute phase hemorrhage volume did not correlate with RAP ($r = .07$, $P = .76$) on the affected side. Two weeks later RAP showed significant correlation with the hemorrhage volume ($r = .44$, $P = .04$) (Fig 3).

Discussion

The main observations of this study are as follows: (1) Hemorrhage volume significantly decreased, while edema and hemorrhage + edema volumes increased after 2 weeks. With the exception of PI (which was higher on the affected side), all TCD

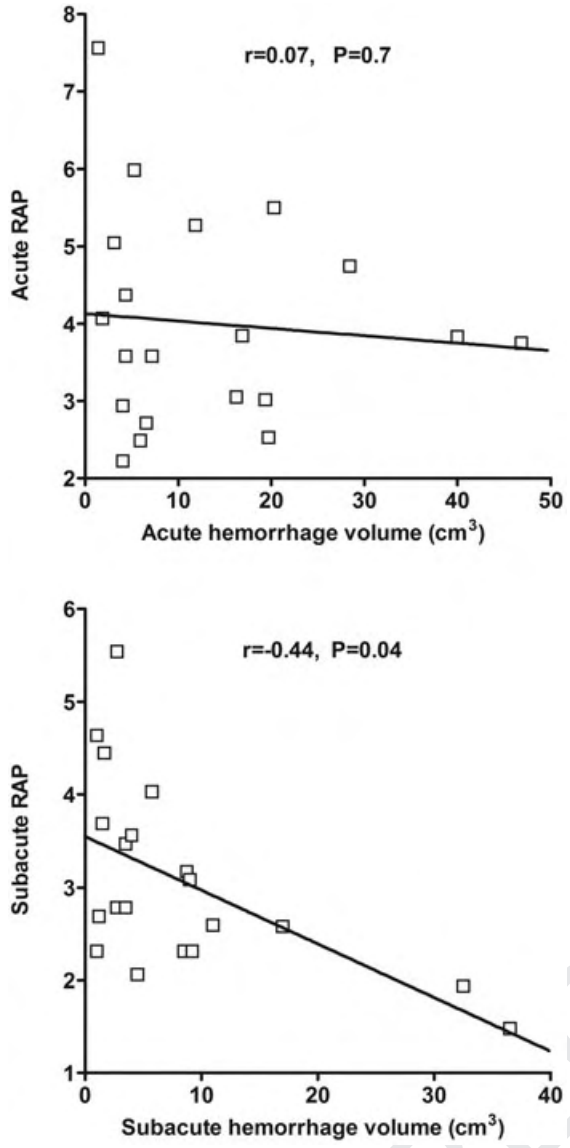

Fig 3. Correlations between hemorrhage volume and RAP in the acute and subacute phases of ICH.

parameters (mean, systolic, diastolic blood FV) were significantly less on the ipsilateral side compared to those on the contralateral side during both examinations. MAP decreased after 2 weeks, consequently CPP and RAP also decreased significantly on both sides, CBFI remained constant on both sides between the two examinations. (2) Hemorrhage volume correlated with the SNSS scores at the first and second examinations as well. Hemorrhage volumes correlated with ipsilateral/contralateral PI ratios and with RAP at the second examination. (3) During the 2-week period the volume of ICH decreased significantly, the clinical status improved without any improvement of ipsilateral velocities and PI. Similarly, to the first examination, in the subacute phase CPP was the same on both sides, while RAP was higher and CBFI was lower on the affected side.

Sudden appearance of a new mass (hemorrhage) temporarily compromises the cerebral blood flow on the affected side of the brain. As ICP increases, CPP falls, diastolic and mean blood FVs decrease and PI increases[18,19]. Studies in patients with traumatic ICH[20,21,33] have shown, that these effects are usually more pronounced in the ipsilateral hemisphere, presumably reflecting ICP gradients related to compartmentalized mass effect. In this study, the interhemispherial differences in the mean, systolic, diastolic FVs were significant during the acute phase and 2 weeks after hemorrhagic stroke. On the affected side, the FVs were lower and the PI was higher than on the nonaffected side during both examinations. When comparing TCD parameters of patients with intracerebral hematomas and control individuals, Egido et al observed that there was not only an interhemispherial difference in FVs, but FVs were lower in both hemispheres in the patients compared to controls.[34]

Although MAP decreased and the clinical status improved significantly after 2 weeks, our TCD results did not reflect these changes: the absolute values (mean, systolic, diastolic FV, and PI) did not change significantly in the course of 2 weeks on either the affected or the nonaffected sides. Therefore, we used RAP, CPP, and CBFI, for better understanding the hemodynamic changes taking place around the hematoma area. In the acute phase, the RAP was higher and the CBFI was lower on the affected side, whereas the CPP was similar in both sides. Presumably, the hemorrhage compressed the surrounding small vessels resulting in an increased RAP on the ipsilateral hemisphere. This increased resistance led to a decreased CBFI in relation with the nonaffected side. Comparison of the CPP, RAP, CBFI values for the same side showed, that CPP and RAP decreased significantly, and that CBFI remained the same for both sides after 2 weeks as well. Decrease in CPP could be partly explained by the decrease of MAP (17.5%), which was attributed to the initiated antihypertensive treatment of these patients. To retain a constant CBFI during decreasing systemic blood pressure, RAP had to decrease in a similar magnitude. Our results show that RAP around the MCA territory actually decreased sufficiently enough to keep up with the CPP changes. The exact mechanism of the RAP decrease is not known, but we assume that arteriolar vasodilation occurs in this territory to compensate for the decreased CPP, which is attributed to the blood pressure lowering therapy.

Autoregulation of blood flow denotes the intrinsic ability of an organ or a vascular bed to maintain a constant perfusion in the face of blood pressure changes. Cerebral autoregulation is diminished in severe head injury,[35] or acute ischemic stroke,[36] leaving the surviving brain tissue unprotected against the potentially harmful effect of blood pressure changes. Likewise, autoregulation may be impaired in the set of a space-occupying brain lesion, for example, a tumor,[37] a hemorrhage,[38] or it can be diminished by just a minor head injury as well.[39] Previously Reinhard et al observed that cerebral autoregulation is primarily preserved in acute ICH, but a secondary decline mainly ipsilateral to the ICH can occur, being associated with poor clinical status, ventricular hemorrhage, lower CPP and worse clinical outcome.[40]

As it is shown in Tables 3 and 4, FVs and CBFI were considerably lower on the affected, than on the nonaffected side during the acute phase. The maintenance of CBFI despite decreasing CPP indicates sufficiently effective autoregulatory mechanisms

in the MCA territory of the affected side. Previously, it has been stated that the brain is capable of preserving autoregulation during small to middle size hemorrhagic strokes.[41] This is in accordance with our results, as all patients included in our study had hemorrhages of these size categories. The clinical status of our patients improved significantly as expected by the improved SNSS scores, however, it remains unknown, whether the survival of these patients with small-middle size ICH can be explained by an intact autoregulatory mechanism.

In the study performed by Tang et al, patients with greater ICH volume had a higher PI of the ipsilateral MCA compared to those with ICH volume less than 25 mL.[42] According to Mayer et al in hemorrhages smaller than 25 mL, the PI ratio did not correlate with the hematoma volume, while ipsilateral PIs were consistently elevated and mean velocities consistently depressed when intracerebral hemorrhage volumes exceeded 25 mL. Furthermore elevated ratios of ipsilateral-to-contralateral pulsatility correlated strongly with hemispheric lesion volume.[43] As it was shown on Figure 2, the ipsilateral/contralateral PI ratio did not correlate with the hemorrhage volume during the first examination. This result is in agreement with the findings of Mayer et al, as the majority of our measured hemorrhages were smaller than 25 mL. On the contrary, during the second examination the ipsilateral/contralateral PI ratio correlated with the hemorrhage volume. This observation points out the fact, that in the subacute phase large hemorrhages are accompanied by large PI asymmetry, indicating that the 2-week duration is not long enough for the total compensation of altered hemodynamic status. Bellner et al evaluating PI in patient with different intracranial pathologies (subarachnoid hemorrhage, closed head injury, etc.) observed, that PI correlated strongly with ICP independently of the underlying pathology.[44] In another study, when evaluating the prognostic value of PI in acute ICH, Martí-Fàbregas et al observed that the PI of the unaffected hemisphere was correlated with mortality, therefore the authors stated, that PI may be a predictor of death in acute ICH.[45] In a second study of the same group, a positive correlation between TCD parameters and ICH total volume and hypoattenuating volume surrounding the hematoma on CT was reported.[46]

The TCD asymmetries detected in our patients most likely implicate compartmentalized pressure gradients, although these asymmetries did not correlate with the amount of blood volume in the tissue, as none of the hemodynamical parameters showed a close correlation with the volume of acute bleeding. The edema volume doubled during the 2 weeks period and the total lesion volume increased by approximately 50% without any further worsening of hemodynamic parameters. It can be assumed, that not the perilesional edema, nor the total lesion volume, but the extravasated blood itself has the pronounced effect on the TCD parameters. Besides, it is not only the compartmentalized ICP gradients, but also the vasoconstrictive effect of the bleeding, which might result in drastic changes in cerebrovascular parameters recorded in the ipsilateral and contralateral hemispheres.

We demonstrated that hemorrhage volumes correlate with RAP values in the subacute phase. In other words, the larger the hemorrhage, the lower the RAP. This means that in case of large hemorrhages the affected side is able to decrease RAP significantly enough to enable the better perfusion of the particular area, accompanied with a faster resolution of the symptoms. Although, it is known that red blood cells (RBC) play a potentially important role in delayed edema development after ICH since oxyhemoglobin release–a consequence of RBC lysis–is a potent vasoconstrictor,[47] our results indicate that the autoregulation mechanisms are capable of overwhelming the expected vasoconstrictions.

There are some limitations of this study. The high rate of mortality led to the inclusion of a selected patient group of ICH survivors with small hematoma volume, resulting in a total number of 20 patients. During the various comparisons between different parameters no adjustment was performed. These might influence the interpretation of our results.

In summary, it can be stated, that absolute velocities measured with TCD may not be sufficient enough to describe cerebral hemodynamics, because they do not take into account the systemic blood pressure changes. CPP, RAP, and CBFI are more informative for the better understanding of the underlying pathophysiological processes in ICH. Second, after an initial deterioration, cerebral autoregulation is preserved in small brain hemorrhages. Finally, it is not only the hemorrhage or the edema volume, but also the interaction of autoregulatory mechanisms and vasoactive substances, which contribute to the clinical outcome of patients with ICH.

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Queries

Q1 Author: Please check authors' affiliations and details of the corresponding author as typeset for correctness.

Q2 Author: Please check "Disclosure" statement for correctness.