Doppler Pulsatility Index in Spontaneous Intracerebral Hemorrhage

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Key Words

Transcranial duplex sonography · Pulsatility index · Midline shift · Intracerebral hemorrhage · Functional outcome

Abstract

Background and Purpose: Elevated intracranial pressure (ICP) as a result of intracerebral hemorrhage (ICH) and perihematomal edema often leads to tissue shift, which can be identified in cross-sectional imaging and presents a known predictor of functional outcome. Pulsatility indices (PIs) of the intracranial arteries as measured by transcranial Doppler sonography (TCD) may serve as surrogate parameters for ICP. This study aims to investigate whether PI correlates with ICP and midline shift and serves as a reliable predictor of functional outcome in patients with ICH. **Methods:** Within a 1-year period between April 2009 and April 2010, 136 patients with acute spontaneous, supratentorial ICH were admitted to our tertiary care hospital. One-hundred and twenty-four patients fulfilled the inclusion criteria and were eligible for analysis. TCD and transcranial duplex sonography were performed on admission and at least once more during hospital stay. Functional outcome was assessed 6 months after discharge. Correlation analyses, logistic regression analyses and receiver operating characteristic curves were calculated. **Results:** One-hundred and twenty-four patients were included in the analysis. Six-month mortality amounted to 39.5%. The ICH score and PIs of the middle cerebral artery were independent predictors of outcome 6 months

after discharge. **Conclusions:** Early PI monitoring by TCD correlated with ICP and may be used to predict the outcome after 6 months.

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Introduction

Spontaneous intracerebral hemorrhage (ICH) is associated with severe morbidity and a 30-day mortality rate of up to 55% [1]. Possible complications include hematoma growth, perihematomal edema and intraventricular hemorrhage [1]. These complications may lead to elevated intracranial pressure (ICP), either primarily through an increase in intracranial volume or secondarily through acute obstructive hydrocephalus. Reduction in elevated ICP maintaining values <20 mm Hg is the major therapeutic target to prevent potentially life-threatening cerebral hypoperfusion [1–5]. ICP can be monitored indirectly by cross-sectional imaging as well as directly by ventriculostomy and microtransducers [6]. However, marked and clinically relevant ICP gradients may exist within the supratentorial department [7–11], possibly resulting in locally rather than globally measured ICP.

Transcranial Doppler (TCD) and duplex sonography (TDS) present noninvasive, inexpensive bedside tools to diagnose and monitor intracranial pathology such as midline shift (MLS), cerebral artery flow velocities and, in special cases, hematoma volume [12–15] and is therefore

Fig. 1 **a** MLS evaluated by TDS: insonation through the left temporal bone window. V3 = Third ventricle; T = thalamus; B = distance between the right tabula of the skull and the middle of the third ventricle. **b** Distance from the left/right tabula of the skull/TDS probe and the middle of the third ventricle (A/B).

applicable in patients with cerebral ischemia, subarachnoid hemorrhage and ICH [12, 13, 15–18]. Furthermore, elevated ICP may be detected by increased PI [19], which is not only more easily accessible than direct ICP measurement through ventriculostomy or microtransducers in the majority of patients but may also represent the ICP of a larger part of the supratentorial compartment due to the course of the respective intracranial vessel.

This study aims to investigate whether PI measured by TCD is a valid surrogate for ICP and whether PI correlates with functional outcome after 6 months in patients with supratentorial ICH.

Materials and Methods

Patients and ICH Management

This study was performed at a tertiary University Hospital (Erlangen, Germany). All patients with spontaneous, supratentorial ICH who were admitted between April 2009 and April 2010 were eligible. One-hundred and thirty-six patients were screened. Twelve patients were not enrolled due to the following exclusion criteria: insufficient temporal bone window ($n = 3$), early hematoma growth ($n = 4$) and hematoma evacuation ($n = 5$). Patients with hematoma growth and/or hematoma evacuation were excluded since the change in intracranial volume would have prejudiced the prediction analysis.

ICH management was carried out according to EUSI recommendations [20]. Hematoma volume was calculated from cardiac CT (cCT), as previously described [21, 22]. Hematoma growth was defined as an increase of more than 33% in the parenchymal hematoma volume compared to the baseline hematoma volume [23].

Outcome Assessment

Functional outcome was evaluated 6 months after discharge using the modified Rankin Scale (mRS). The mRS was assessed by a semistructured telephone interview by a certified interviewer with the patient or – if the patient was unable to talk on the phone – the legal guardian.

Standard Protocol Approval, Registration and Patient Consent

Consent to participate in this study was obtained from all patients or their relatives/legal guardians. The study was approved by the local ethics committee.

Neurosonologic Methods

All TCD examinations were carried out by a dedicated trial team independent of the clinical team. All investigators were experienced neurosonologists and are certified for neurological vascular ultrasound by the German Ultrasound Society. TCD was conducted within 24 h of symptom onset, after 3–6 days and again after 8–12 days with a conventional Doppler system (SONARA/tek, Medilab, Würzburg, Germany) equipped with a 2-MHz pulsed wave probe. Whenever possible, TCD was conducted just before cross-sectional imaging. Within the standardized study protocol, the middle cerebral artery was examined on both sides between depths of 45 and 65 mm. PI was calculated (systolic velocity – diastolic velocity/mean flow velocity) and judged normal if values between 0.5 and 1.19 were reached [24]. The maximum PI in the middle cerebral artery was entered in the analysis.

TDS was performed at the same time points as the TCD examinations with a phased-array ultrasound system equipped with a 1.33-MHz transducer (Siemens Acuson Antares) through the contralateral temporal bone window as described before [12, 18]. The third ventricle was visualized in a depth of 6–8 cm and identified by its parallel hyperechogenic margins and the surrounding hypoechogenic thalami. The distance between the probe and the margins of the third ventricle were measured in perpendicular lines. The deviation from the presumed midline was measured by the equation $(a - b)/2$ (fig. 1) [18].

Statistics

Statistical tests were two-sided and the significance level was set at $\alpha = 0.05$. The distribution of the data was assessed with the Kolmogorov-Smirnov test. Continuous and categorical variables are expressed as the mean and SD, interquartile range, or as percentage, as appropriate. We performed forward step-wise logistic regression analyses as well as receiver operating characteristic (ROC) curves with functional outcome (mRS 0–2, mRS 3–6) and mortality at 6 months after discharge as the dependent variables. All statistical analyses were calculated with the SPSS 17.0 software package (SPSS Inc., Chicago, Ill., USA).

Table 1. Demographic and clinical data of all patients and depending on functional outcome after 6 months

	All (n = 124)	mRS 0–2 (n = 15)	mRS 3–6 (n = 109)	mRS 6 (n = 49)
Mean age $\pm$ SD, years	66 $\pm$ 12	62 $\pm$ 19	67 $\pm$ 12	69 $\pm$ 15
Females	57 (46.0)	8 (53.3)	49 (45.0)	21 (42.9)
Mean LOS $\pm$ SD, days	17 $\pm$ 11	7.5 $\pm$ 6	19 $\pm$ 9	18 $\pm$ 12
Median LOV, days	9.5 [0–20]	0 [0–3]	10 [0–20]	12 [3–23]
Median NIHSS at admission	18 [12–37]	6 [3–10]	18 [12–37]	34 [16–37]
Median mRS before ICH	0.5 [0–1]	0 [0–0.5]	1 [0–2]	1 [0–2]
Median mRS after 6 months	5 [3–6]	2 [1–2]	5 [3–6]	6
Hematoma localization, right	66 (53.2)	7 (46.7)	59 (54.1)	27 (55.1)
Hematoma localization, loco typ	76 (61.3)	9 (60.0)	67 (61.5)	32 (65.3)
Median hematoma volume, cm ³	28 [20–51]	14 [8–21]	28 [16–60]	43 [26–69]
Ventricular involvement	51 (41.1)	2 (13.3)	49 (45.0)	26 (53.1)
Median PI at day 0, ipsilateral	1.4 [1.2–1.9]	1 [0.9–1.2]	1.8 [1–2.9]	2.2 [1.6–3.1]
Median PI highest ever, ipsilateral	1.8 [1.3–2.6]	1 [1–1.3]	1.8 [1.2–2.9]	3.1 [1.9–3.8]
Median MLS at day 0	2 [0–5]	0 [0–0]	2 [0–5]	4 [1–7]
Median MLS highest ever	4 [0–10]	0 [0–0.5]	5 [0–12]	11 [4–16]

Figures in parentheses are percentages; figures in brackets are interquartile ranges. LOS = Length of stay; LOV = length of ventilation; loco typ = loco typico.

Results

During a 1-year period, 124 patients with spontaneous ICH were enrolled in this study. The median National Institutes of Health stroke scale on admission was 18, the mean hematoma volume was 28 cm³. The demographic and clinical data of the patients are given in table 1. Mortality 6 months after discharge amounted to 39.5%.

Correlation of PI and ICP and MLS, Respectively

Fifty-nine patients received invasive ICP monitoring (via ventriculostomy, n = 56, or microtransducer, n = 3). PI was correlated with ICP during the examination. A total of 137 examinations were analyzed (59 at admission, 54 between day 3 and day 6, and 24 between day 8 and day 12). The correlation of PI with ICP was high ($r = 0.712$). Additionally, the correlation of PI and MLS was calculated in those patients (n = 85) who had cross-sectional imaging (cCT or cardiac MRI) within 1 h of TCD (49 at admission, 27 between day 3 and day 6, and 9 between day 8 and day 12). The correlation of PI and MLS was high ($r = 0.645$).

Predictors of Functional Outcome

The parameters age, sex, length of hospital stay and hematoma location did not show statistically significant differences between survivors and nonsurvivors. The following parameters were significantly associated with mortality in the univariate analysis: higher National Institutes of Health stroke scale on admission, prolonged

length of ventilation, ventricular involvement of ICH, larger ICH volume, increased MLS on admission and follow-up examinations, higher ICH score and higher PI of the affected and unaffected hemisphere on admission and follow-up examinations. Furthermore, PI was associated with a poor outcome (mRS 3–6) and mortality. The results of the multivariate logistic regression analysis depending on functional outcome are given in table 2. MLS was not included in the multivariate analysis since our calculations showed that MLS and PI closely correlate with each other in this patient cohort.

Sensitivity, Specificity, Positive and Negative Predictive Values for Mortality

ROC analyses (specificity and sensitivity) as well as positive and negative predictive values for critical PI values, indicating mortality after 6 months, were calculated. ROC analyses showed that PI predicted for mortality within 6 months after discharge. The results of the ROC analyses as well as the positive predictive values and negative predictive values depending on PI cut-off values are given in table 3.

Discussion

Formation of perihemorrhagic edema is dynamic [25, 26], may last up to 14 days [27] and may peak in the early as well as in the subacute phase [18, 28], leading to an

Table 2. Multivariate logistic regression analysis depending on mRS 6 months after discharge

	mRS 0–2			mRS 3–6			mRS 6		
	Exp (coef)	95% CI	p	Exp (coef)	95% CI	p	Exp (coef)	95% CI	p
ICH score	0.485	0.237–0.956	0.027	2.154	1.365–3.267	0.039	4.459	1.843–8.632	<0.001
Length of ventilation	0.852	0.384–1.952	0.184	1.037	0.638–2.825	0.732	1.227	1.097–1.484	0.156
PI highest ever, ipsilateral	0.117	0.012–1.238	0.079	1.871	1.017–3.954	0.046	3.991	2.054–7.264	<0.001

Statistically significant predictors are given in italics. CI = Confidence interval.

increase in ICP that can cause subfalcial and uncal herniation. However, increased ICP may not only appear directly as tissue shift which can be imaged in cross-sectional imaging or TDS, but also indirectly as decreased end-diastolic flow velocity leading to characteristic changes in the Doppler waveform and increased PI [29] (fig. 2).

This prospective study is solely based on ultrasound imaging. PI is known to vary depending on the resistance of the supplied tissue, the diastolic velocity of the basal cerebral arteries decreasing in case of increased ICP and thus elevating the PI [14]. Furthermore, age can cause the vessels to loose compliance; hence, older people may have increased PIs, independently of increased ICP. In order to rule out old age as an underlying reason for increased PI in our cohort, we compared the PIs of patients older and younger than 65 years, after adjusting for MLS and hematoma volume, and found no significant difference concerning PI and age. Intracranial tissue shift is generally monitored by serial cCT scans. However, this involves the repeated transportation of critically ill, possibly ventilated and unstable patients, which may lead to complications in up to 70% [30]. Alternatively, intracranial MLS can be reliably monitored by TDS with a high inter- and intraobserver reliability [13, 31, 32], thus providing a noninvasive, bedside alternative to cCT.

In this study, normal ipsilateral PI as well as slight to moderate elevation of PI (PI <1.75) indicated that the patient survived the follow-up period (negative predictive value >80%; table 3), whereas initial high PI (PI >2.0) had a high predictive value of >96% for mortality within 6 months of discharge. Our data are in line with the results of previous studies showing that the PI as well as MLS serve as predictors of functional outcome [29, 33, 34].

TDS is an inexpensive, bedside tool that can easily be implemented and interpreted.

The main fields of application are the detection of stenoses of the basal cerebral arteries and the evaluation of vasospasms [35, 36]. Furthermore, TDS measurement

Table 3. Sensitivity (%), specificity (%), positive and negative predictive values (%) of day 0 and the highest PI of the affected hemisphere, respectively, for mortality after 6 months

Cut-off PI	Sensitivity	Specificity	PPV	NPV
Day 0 (AUC 0.856, CI 0.779–0.932)				
1.25	83.7	46.7	50.6	81.4
1.35	83.7	65.3	61.2	86.0
1.45	79.6	74.7	67.2	84.8
1.55	77.6	90.7	84.4	86.1
1.65	65.3	92.0	84.2	80.2
1.75	65.3	93.3	86.5	80.5
1.85	61.2	96.0	90.9	79.1
2.00	57.1	98.7	96.6	77.9
2.15	53.1	100.0	100.0	76.5
Highest (AUC 0.886, CI 0.823–0.949)				
1.45	91.8	46.7	52.9	89.7
1.55	87.8	61.3	59.7	88.5
1.70	85.7	72.0	66.7	88.5
1.85	77.6	82.7	74.5	84.9
1.95	71.4	88.0	79.5	82.5
2.05	71.4	92.0	85.4	83.1
2.15	67.3	96.0	91.7	81.8
2.35	65.3	96.0	91.4	80.9
2.55	61.2	97.3	93.8	79.3

PPV = Positive predictive value; NPV = negative predictive value; AUC = area under the curve; CI = confidence interval.

can be used in the assessment of brain death [37]. In the present study, we measured PI and MLS as surrogate parameters for increased ICP at different time points, covering the initial and subacute phase of edema formation. In comparison to invasive ICP monitoring, which may lead to complications such as hemorrhage and infection [38–40], PI monitoring is noninvasive, and thus, does not cause complications. Moreover, costs of ventriculostomy and the installation of microtransducers by far exceed those of TCD. However, ICP monitoring via

Fig. 2. CT scans, TDS and TCD of patients with different characteristic forms of ICH and the according Doppler waveform changes and increased PIs. TDS was performed through the right temporal bone window in each case. SFV = Systolic flow velocity; DFV = diastolic flow velocity; MFV = mean flow velocity.

TCD is less accurate than invasive monitoring and – while extraventricular drains and microtransducers measure ICP continually – ICP monitoring by TCD covers only a limited time period. Thus, ICP monitoring by PI may not replace invasive ICP monitoring, but may be of diagnostic help in patients with suspected elevated ICP who are not suitable for direct ICP measurement or in which the indication to apply direct ICP measurements is questionable.

Limitations of our study comprise the small patient number and the single-center design. Furthermore, monitoring of PI and MLS by ultrasound depends on the existence of sufficient temporal bone windows, which will always present an obstacle in intracranial ultrasound, even though this restriction becomes less frequent with the advances of ultrasound technology.

Conclusion

This prospective ultrasound study shows a high correlation between PI and MLS and ICP, respectively. Therefore, we suggest that TCD may be used as a screening parameter for patients with ICH in risk of ICP elevation in addition to the usual monitoring. Furthermore, measurement of PI and MLS may serve as reliable though indirect tools to predict mortality at 6 months.

Disclosure Statement

There is no conflict of interest.

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