Vasospasm in Intracerebral Hemorrhage with Ventricular Involvement: A Prospective Pilot Transcranial Doppler Sonography Study

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Key Words

Ultrasound · Vasospasm · Intracerebral hemorrhage ·
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Abstract

Background: Cerebral vasospasm (VSP) is a common complication after subarachnoid hemorrhage (SAH), but has rarely been reported after intracerebral hemorrhage (ICH) without subarachnoidal bleeding. The underlying pathophysiological mechanism is mainly mediated by circulating heme products within the cerebrospinal fluid, and thus patients with ICH and ventricular involvement (IVH) may also be in danger of developing VSP. The incidence and role of VSP in IVH, however, have not been systematically studied. **Methods:** We prospectively enrolled 115 patients with ICH with or without IVH into the study between April 2009 and April 2010. All patients received serial extracranial and transcranial Doppler sonography (TCD) at baseline, on days 3–5 and 7–9 to detect and monitor VSP. In addition, CT scans taken on admission, after 24 h and before discharge were evaluated for the occurrence of delayed cerebral ischemia. **Results:** Three out of 53 patients (5.7%) with IVH showed a significant elevation of flow velocities over the examined timeframe. One of these patients developed severe VSP re-

sulting in secondary ischemic infarction. None of the ICH patients without IVH showed significantly elevated flow velocities or secondary infarction. **Conclusions:** Cerebral VSP with secondary infarction may occur in patients with spontaneous IVH, though far less frequently than in SAH; thus, systematic screening of all patients with IVH may not be warranted. However, serial TCD should be considered in patients with secondary clinical worsening or extensive IVH.

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Introduction

In the management of subarachnoid hemorrhage (SAH), cerebral vasospasm (VSP) is a frequent complication that develops in more than 60% of patients between days 3 and 8. Only about 30% of patients with VSP become symptomatic [1, 2]. Although the mechanism of the development of VSP is not fully understood, the main hypothesis is that heme products circulating in the subarachnoid space lead to vasoconstriction via multiple distinct pathways [3]. In primary intracerebral hemorrhage (ICH) with ventricular involvement (IVH), heme products also reach the subarachnoid space through cerebrospinal fluid (CSF) circulation, although at a lower con-

centration. Thus, it is conceivable that these patients are also in danger of developing VSP. However, delayed ischemic neurological deficit (DIND) and delayed cerebral ischemia (DCI) caused by VSP are not frequently observed in this patient population. Possible explanations are that the lower concentration of circulating heme products are insufficient to cause VSP in IVH or that VSP are milder, not leading to DCI with distinct DIND, but possibly to a clinically not as evident permanent hypoperfusion. Several case presentations of VSP in IVH leading to secondary infarctions are reported in the literature [4–8]; however, a systematic investigation regarding the incidence of VSP in this population has not yet been conducted. We performed a prospective study to evaluate the frequency and clinical relevance of VSP using serial ultrasound examinations and analysis of standard CT scans in patients with ICH with or without IVH.

Methods

Patients and Management

Patients with spontaneous ICH (n = 115) were enrolled into the study in the predefined 1-year study period (4/2009–4/2010). Patients with evidence of SAH or other forms of secondary hemorrhage (i.e. arteriovenous malformations) were not included in this study. In addition, patients undergoing early hematoma evacuation and those who received do not treat/resuscitate orders within 24 h of admission were also excluded. Treatment of ICH was conducted according to international guidelines [9]. Intraventricular treatment with rt-PA as well as the management of extraventricular and lumbar drainages was conducted according to previously published institutional protocols [10]. All patients with occlusive hydrocephalus received extraventricular drainages. CSF cell counts as well as microbiological analyses were performed at regular intervals in order to exclude infection. In all ventilated patients, pCO₂ was measured at regular intervals and was kept between 35 and 45 mm Hg whenever possible.

Standard Protocol Approval, Registrations and Patient Consents

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.

Neurosonological Methods

All transcranial Doppler sonography (TCD) examinations were carried out by a dedicated trial team independent of the clinical ICU team. All investigators were experienced neurosonologists and certified for neurological vascular ultrasound by the German Ultrasound Society (DGKN/DEGUM). Extra- and transcranial Doppler sonography was conducted at baseline (within 24 h of symptom onset), after 3–5 days and again after 7–9 days with a conventional Doppler system (Sonara/tek; Medilab, Würzburg, Germany) equipped with a 2-MHz (pulsed wave) and a 4-MHz (continuous wave) probe. Within the standardized study

protocol, first the middle cerebral artery (MCA) was examined on both sides between depths of 45–65 mm. In addition, the anterior cerebral artery was insonated between 60 and 75 mm, the posterior cerebral artery between 60 and 75 mm and the basilar artery between 70 and 110 mm to detect VSP not affecting the MCA. The respective maximum flow velocity was used for the analysis. However, while TCD of the MCA has a reasonable positive and negative predictive value for predicting angiographic vessel narrowing, it is less useful for other intracranial vessels [11]. Therefore, only MCA velocities were entered in the analysis. Flow velocities (cm/s) within the MCA were calculated using an established and validated conversion formula [flow velocity (cm/s) = 40 × Doppler frequency (kHz)] [12, 13]. Once VSP were diagnosed, daily TCD monitoring was initiated and continued until intracranial velocities had normalized.

Diagnosis of Vasospasm

Diagnosis of VSP was based on both velocity and Lindegaard ratio, as recommended [14–17]. Severity of VSP was divided into three groups: (1) mild VSP defined as an increase of >50% in the baseline velocity per day between baseline and follow-up examination with a mean velocity <160 cm/s and a Lindegaard ratio (V_{MCA}/V_{ICA}) between 2 and 6 [18]; (2) moderate VSP with a mean velocity above 160 cm/s and Lindegaard ratio above 6 (± 0.3) [14, 16], and (3) severe VSP with velocities >200 cm/s and Lindegaard ratio above 6 (± 0.3) [14, 16].

Computed Tomography

No study specific CT scans were performed. However, according to international and institutional guidelines [9], CT scans were carried out on admission, after 24 h to rule out hematoma growth as well as prior to discharge. In addition, following an institutional protocol, all patients received CT angiography on admission to rule out potential underlying vascular pathology (i.e. arteriovenous malformations, aneurysms). Later follow-up CTs were done at the discretion of the treating physician depending on the clinical condition of the patient. All CT scans were analyzed for potential secondary cerebral infarctions.

ICH volume was calculated using the formula for ellipsoids ABC/2 [19, 20]. Regarding the low reliability and feasibility of quantitative volumetry in IVH [21], the intraventricular blood portion was not considered for hematoma volume measurement.

Statistics

Statistical analysis was performed with the SPSS 17.0 software package. The significance level was set at $\alpha = 0.05$. Statistical tests were two-sided. Distribution of the data was assessed with the Kolmogorov-Smirnov test. Normally distributed data are presented as means $\pm$ SD. Other data are presented as medians and IQR.

Results

Study Population and Baseline Characteristics

A total of 115 patients with spontaneous ICH were prospectively enrolled into this study between 4/2009 and 4/2010. One patient with ICH had insufficient tem-

Table 1. Clinical and demographic data of patients

	ICH group (n = 61)	IVH group (n = 53)	p	VSP patients (n = 3)
Age, years	62 (52–74)	70 (59–76)	0.08	60 (56–68)
Female	24 (39.3)	25 (47.2)	0.45	1 (33.3)
ICH volume, cm ³	25 (18–51)	41 (24–67)	0.03	13 (11–35)
IVH: lateral ventricle(s)	–	51 (96.2)	–	3 (100)
IVH: third ventricle	–	31 (58.5)	–	3 (100)
IVH: fourth ventricle	–	22 (41.5)	–	3 (100)
Occlusive hydrocephalus	–	38 (71.7)	–	2 (66.7)
Length of hospital stay, days	11 (9–14)	16 (9–21)	<0.01	22 (19–39)
Mechanical ventilation	31 (50.8)	33 (62.3)	0.26	3 (100)

Data presented as medians (IQR) or n (%). p values refer to ICH vs. IVH group.

poral bone window, and was therefore excluded from the analysis. Hence, 114 patients remained eligible for participation in this study, 53 (46%) with ventricular involvement (IVH group) and 61 (54%) patients with isolated parenchymal hemorrhage (ICH group). The demographic and clinical data of the patients are given in table 1.

Incidence of VSP

None of the patients with ICH without IVH showed elevation of flow velocities. In contrast, the incidence of VSP in the IVH group was 5.6% (3/53; CI: 0–12/53). A 58-year-old man with hypertensive deep ICH with extensive IVH developed moderate VSP in the left MCA (contralateral to the ICH) on day 5 after onset, progressing into severe VSP on day 7 (fig. 1). Because of the ongoing sedation and ventilation of the patient, a clinical worsening was not observed. However, a follow-up CT scan on day 9 showed left-sided DCI (fig. 1, arrow).

Two patients developed mild VSP after 3–5 days. No specific treatment was initiated and follow-up examinations did not reveal progression of VSP (fig. 2) or clinical deterioration. All three patients with VSP had extensive IVH affecting all ventricles with large intraventricular blood volume.

Incidence of DCI

None of the patients in the ICH group and only 1 patient in the IVH group (1/53; 1.9%) showed DCI on follow-up CT scans. The only patient with DCI was the patient with severe VSP in ultrasound screening. The infarction was detected 4 days after VSP became apparent in ultrasound screening (fig. 1).

Discussion

Cerebral VSP are a common complication after SAH, but have rarely been reported in ICH without subarachnoidal bleeding. Most reports on VSP in non-subarachnoidal ICH show occurrence mainly in the context of arteriovenous malformations [5–8, 22], but also in spontaneous hypertensive IVH [4]. Following pathophysiological considerations with heme products circulating in the CSF reaching the subarachnoid space, it is conceivable that VSP may occur in IVH patients. With mainly case presentations in the literature, we undertook a prospective study systematically screening for DCI and VSP in patients with spontaneous ICH with and without IVH.

The frequency of VSP after SAH has been the subject of extended research, with more than 60% of patients developing significant VSP and almost one third of those patients becoming symptomatic. The incidence of VSP after spontaneous IVH has not yet been investigated. Dull and Torbey [4] presented the case of a female patient with isolated IVH after administration of heparin for bilateral cerebellar infarction. On day 3 after the IVH, the patient developed VSP; however, no subsequent vasospastic infarctions were detected. Another case report, presented by Gerard et al. [22] described a female patient with isolated IVH caused by a temporal arteriovenous malformations. Angiography revealed VSP in several intracranial arteries resulting in multiple infarctions. Performing a systematical screening for DCI and VSP in ICH patients, our data show that while DCI and VSP after primary ICH do occur, the frequency is much less than after SAH: 3 of 53 patients (5.6%) with IVH and none with

Fig. 1. Flow velocities, Lindegaard ratio and cranial CT scans of the patient who developed VSP over a period of 2 weeks. Please note the ischemic lesion in the left MCA territory (arrow) which developed between days 7 and 9.

mere ICH developed VSP. Only 1 patient, the patient with severe VSP, in the IVH (1.9%) and none in the ICH-only group showed evidence of DCI on follow-up CT scans. This, on the other hand, corresponds to the fact that the only patient with DCI in our series also showed prior severe VSP. Clinically, this would imply ultrasound as a screening method for DCI.

All of the affected patients had extensive intraventricular bleeding involving all ventricles (table 1). It is therefore conceivable that IVH patients with large intraventricular blood volume – and therefore a higher concentration of circulating heme products in the CSF – develop VSP more often than those with only small quantities of IVH. Even though we cannot formally prove this hypothesis because of the small case number of patients with VSP in our study, this observation is in line with previously published data on the prevalence of VSP in SAH patients. Here the amount of subarachnoid blood is a good predictor of DIND/DCI [1, 23–26]. Because of the assumed time-frame of VSP preceding DIND/DCI, serial TCD may serve as a screening tool in patients with extensive intraventricular hemorrhage that cannot be monitored clinically due to severity of neurological deficit.

There are limitations to our study, mainly the small patient number and the single-center design. With only 3 patients developing elevated flow velocities, no firm analyses regarding predictors or risk factors for the development of VSP were possible. Furthermore, rather aggressive protocols regarding intraventricular lysis and drainage of intraventricular blood through extraventricular drainage might have led to a reduced incidence of VSP. Since the majority of patients in our study were sedated and ventilated over the study period due to large ICH, no valid analysis regarding the incidence of DIND was possible. However, it is to our knowledge the first systematic examination on the incidence of VSP and DCI in IVH patients. Another limitation is that for practical and ethical reasons neither serial CT angiographies nor conventional angiography were part of our study design. This mirrors the clinical routine, and TCD is of established value and widely accepted in the detection and monitoring of angiographic vasospasm (type A, class I–II) [16]. It displays a sensitivity and specificity for the diagnosis of symptomatic VSP and subsequent cerebral infarction on CT scans of 70–80% [27–29]. In addition, VSP diagnosis by TCD has a high correlation with the findings on DSA if vessels can be isolated [30].

Fig. 2. Flow velocities, Lindegaard ratio and cranial CT scans of the two patients with mild VSP.

Conclusion

Elevated flow velocities and DCI may occur in patients with spontaneous IVH, though far less frequently than in SAH. Thus, systematic screening of all patients with IVH may not be warranted, but serial TCD should be considered in patients with extensive IVH or secondary clinical worsening.

Disclosure Statement

There is no conflict of interest to report.

References

- Fisher CM, Kistler JP, Davis JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery* 1980;6:1–9.
- Frontera JA, Claassen J, Schmidt JM, Warnterberg KE, Temes R, Connolly ES Jr, et al: Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified Fisher scale. *Neurosurgery* 2006;59:21–27; discussion 27.
- Kolias AG, Sen J, Belli A: Pathogenesis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: putative mechanisms and novel approaches. *J Neurosci Res* 2009;87:1–11.
- Dull C, Torbey MT: Cerebral vasospasm associated with intraventricular hemorrhage. *Neurocrit Care* 2005;3:150–152.
- Kobayashi M, Takayama H, Mihara B, Kawase T: Severe vasospasm caused by repeated intraventricular haemorrhage from small arteriovenous malformation. *Acta Neurochir (Wien)* 2002;144:405–406.
- Kothbauer K, Schroth G, Seiler RW, Do DD: Severe symptomatic vasospasm after rupture of an arteriovenous malformation. *AJNR Am J Neuroradiol* 1995;16:1073–1075.
- Maeda K, Kurita H, Nakamura T, Usui M, Tsutsumi K, Morimoto T, et al: Occurrence of severe vasospasm following intraventricular hemorrhage from an arteriovenous malformation: report of two cases. *J Neurosurg* 1997;87:436–439.
- Park BS, Won YS, Choi CS, Kim BM: Severe symptomatic vasospasm following intraventricular hemorrhage from arteriovenous fistula. *J Korean Neurosurg Soc* 2009;45:300–302.
- Steiner T, Kaste M, Forsting M, Mendelow D, Kwicinski H, Szikora I, et al: 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* 2006;22:294–316.
- Staykov D, Huttner HB, Struffert T, Ganslandt O, Doerfler A, Schwab S, et al: Intraventricular fibrinolysis and lumbar drainage for ventricular hemorrhage. *Stroke* 2009;40:3275–3280.
- Lysakowski C, Walder B, Costanza MC, Tramèr MR: Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm: a systematic review. *Stroke* 2001;32:2292–2298.
- Eicke BM, Tegeler CH, Dalley G, Myers LG: Angle correction in transcranial Doppler sonography. *J Neuroimaging* 1994;4:29–33.
- Widder B, Görtler M: Doppler- und Duplexsonographie der hirnersorgenden Arterien, ed 6. Heidelberg, Springer, 2004.
- Rabinstein AA, Lanzino G, Wijdicks EF: Multidisciplinary management and emerging therapeutic strategies in aneurysmal subarachnoid haemorrhage. *Lancet Neurol* 2010;9:504–519.
- Lindegard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P: Cerebral vasospasm diagnosis by means of angiography and blood velocity measurements. *Acta Neurochir (Wien)* 1989;100:12–24.
- Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E, et al: Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2004;62:1468–1481.
- Vora YY, Suarez-Almazor M, Steinke DE, Martin ML, Findlay JM: Role of transcranial Doppler monitoring in the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. *Neurosurgery* 1999;44:1237–1247, discussion 1247–1248.
- Grosset DG, Straiton J, McDonald I, Cockburn M, Bullock R: Use of transcranial Doppler sonography to predict development of a delayed ischemic deficit after subarachnoid hemorrhage. *J Neurosurg* 1993;78:183–187.
- Huttner HB, Steiner T, Hartmann M, Kohrmann M, Juettler E, Mueller S, et al: Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. *Stroke* 2006;37:404–408.
- Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, et al: The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 1996;27:1304–1305.
- Zimmerman RD, Maldjian JA, Brun NC, Horvath B, Skolnick BE: Radiologic estimation of hematoma volume in intracerebral hemorrhage trial by CT scan. *AJNR Am J Neuroradiol* 2006;27:666–670.
- Gerard E, Frontera JA, Wright CB: Vasospasm and cerebral infarction following isolated intraventricular hemorrhage. *Neurocrit Care* 2007;7:257–259.
- Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, et al: Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. *Stroke* 2001;32:2012–2020.
- Dupont SA, Wijdicks EF, Manno EM, Lanzino G, Brown RD Jr, Rabinstein AA: Timing of computed tomography and prediction of vasospasm after aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2009;11:71–75.
- Dupont SA, Wijdicks EF, Manno EM, Lanzino G, Rabinstein AA: Prediction of angiographic vasospasm after aneurysmal subarachnoid hemorrhage: value of the Hijdra sum scoring system. *Neurocrit Care* 2009;11:172–176.
- Kistler JP, Crowell RM, Davis KR, Heros R, Ojemann RG, Zervas T, et al: The relation of cerebral vasospasm to the extent and location of subarachnoid blood visualized by CT scan: a prospective study. *Neurology* 1983;33:424–436.
- Rabinstein AA, Friedman JA, Weigand SD, McClelland RL, Fulgham JR, Manno EM, et al: Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke* 2004;35:1862–1866.
- Suarez JI, Qureshi AI, Yahia AB, Parekh PD, Tamargo RJ, Williams MA, et al: Symptomatic vasospasm diagnosis after subarachnoid hemorrhage: evaluation of transcranial Doppler ultrasound and cerebral angiography as related to compromised vascular distribution. *Crit Care Med* 2002;30:1348–1355.
- Wintermark M, Ko NU, Smith WS, Liu S, Higashida RT, Dillon WP: Vasospasm after subarachnoid hemorrhage: utility of perfusion CT and CT angiography on diagnosis and management. *AJNR Am J Neuroradiol* 2006;27:26–34.
- Sloan MA, Haley EC Jr, Kassell NF, Henry ML, Stewart SR, Beskin RR, et al: Sensitivity and specificity of transcranial Doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. *Neurology* 1989;39:1514–1518.