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Prediction of Cerebral Vasospasm Using Early Stage Transcranial Doppler

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Abstract

Transcranial Doppler (TCD) is widely used to monitor vasospasm after subarachnoid hemorrhage (SAH), but its ability to predict the future occurrence of the symptomatic vasospasm (SVS) remains controversial. We investigated the utility of TCD for predicting the future occurrence of SVS after SAH in 45 patients with aneurysmal SAH. TCD was performed on days 1, 3, 5, 7, 10, and 14 after SAH. The mean flow velocity (MFV) of the horizontal portion of the middle cerebral artery (M_1) was recorded. SVS occurred in 24.4% of patients (n = 11). MFV of M_1 increased progressively in patients with SVS, but did not increase in patients without SVS. The mean MFV values were significantly higher in patients with SVS than in patients without SVS (p = 0.031). The mean MFV value on day 3 was already significantly higher in patients with SVS than in patients without SVS (88.5 cm/sec versus 62.7 cm/sec, respectively) (p = 0.018). The receiver operating characteristic curve of MFV on day 3 showed the threshold of 72.5 cm/sec for predictive value of SVS in the future (sensitivity 71.4%, specificity 68.1%, and accuracy 82.3%). Increased MFV of M_1 during the early stage of SAH may predict the future occurrence of SVS. The threshold value of 72.5 cm/sec MFV of M_1 on SAH day 3 was one of the best predictor of future SVS. To prevent delayed cerebral ischemia, aggressive treatment for vasospasm is needed for patients with increased MFV in the early stages of SAH.

Key words: subarachnoid hemorrhage, vasospasm, transcranial Doppler, mean flow velocity, prediction

Introduction

Symptomatic vasospasm (SVS) is a serious complication of aneurysmal subarachnoid hemorrhage (SAH).[27] Poor outcome is associated with the development of neurological deterioration associated with cerebral vasospasm, which can be detected on angiography in 70% of patients with ruptured intracranial aneurysms.[6,7,12] SVS develops between SAH post-bleed days 3 and 14, and 20% to 40% of patients will develop neurological deficits or infarction caused by delayed cerebral ischemia.[4,21,23,28,32] A strong association exists between angiographic vasospasm and cerebral infarction.[5]

Conventional angiography is the most accurate and reliable method for vasospasm detection. However, cerebral angiography is invasive and carries some risks, making serial examinations impossible to perform.[16] The introduction of transcranial Doppler (TCD) in 1982 has provided a noninvasive approach for the evaluation of cerebral vasospasm and for monitoring the development and resolution of this condition.[1,2,9,24] Acceleration of TCD mean blood flow velocity (MFV) to more than 120 cm/sec provides approximately 80% sensitivity and specificity for the presence of angiographic vasospasm in the proximal middle cerebral artery (MCA).[20] At present, TCD is the most widely used imaging modality for diagnosing vasospasm.[33] Nevertheless, TCD has not been evaluated for predicting the future development of SVS.

The present study investigated the utility of TCD for predicting future development of SVS during the early stages after SAH and to derive the threshold using a statistical approach.

Materials and Methods

Subjects were 98 consecutive patients with aneurys-

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mal SAH admitted to the Neurological Intensive Care Unit of Kawasaki Medical School, between April 2009 and March 2011. The diagnosis of aneurysmal SAH was established on the basis of admission computed tomography (CT) and angiography. Exclusion criteria included secondary SAH from trauma, arteriovenous malformation, mycotic aneurysms, unknown origin, or other causes, age younger than 18 years, death on or before SAH day 4 (because of the low risk of developing vasospasm), admission 4 days after SAH onset, and lack of adequate TCD windows. The study was approved by the hospital Institutional Review Board. Informed consent was obtained from the patients or their family. This study was registered in the University Hospital Medical Information Network (Application number 20110412–235241).

All patients underwent digital subtraction angiography on admission. Selection of treatment with clipping or endovascular coil embolization resulted from a consensus reached between the treating neurosurgeon and the interventional neuroradiologist after analyzing the risks and chances of success of both therapeutic modalities for each particular case. All patients received 0.9% normal saline at a rate of 1 ml/kg per hour and an appropriate dosage of supplemental 5% albumin solution was administered to maintain positive fluid balance and central venous pressure >5 mmHg. All patients received intravenous fasudil hydrochloride every 8 hours from day 4 to day 14. Oral statin and mineral corticoid were not routinely administered. Persistent fever (temperature exceeding 38.5°C) was treated with acetaminophen and surface cooling devices. Angiography was routinely performed on patients in whom SVS developed. Endovascular treatment of vasospasm entailed either intra-arterial chemical vasodilation with fasudil hydrochloride or balloon angioplasty. The decision to perform endovascular intervention was made at the discretion of the neurosurgeons and stroke physicians.

SVS was defined as the development of new focal neurological signs, deterioration of the level of consciousness, or both, when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening (for example, hydrocephalus, intracranial hemorrhage, focal brain swelling, seizures, infection, hyponatremia) had been excluded. The diagnosis of SVS was adjudicated on the basis of consensus of the study team. Angiographic vasospasm was defined as moderate-to-severe arterial narrowing on digital subtraction angiography not attributable to atherosclerosis, catheter-induced spasm, or vessel hypoplasia.

TCD was performed on SAH days 1, 3, 5, 7, 10, and 14 by the independent stroke physician (N.M.) who was not involved in the operation, but who was well-acquainted with TCD examination. The data on SAH day 1 were obtained before the clinical high-risk period for vasospasm, and were used as the baseline for comparison with further TCD examinations. Recordings of the MFV of the horizontal part of the MCA (M_1) were measured through the transtemporal windows using a 2-MHz handheld transducer probe. Using the transtemporal window, the depth of insonation varied between 50 and 60 mm for evaluation of the MCA. The MFV, peak systolic velocity, end-diastolic velocity, and pulsatility index of M_1 were recorded for each TCD examination. The Lindegaard index was not calculated because cervical internal carotid artery velocities were not routinely recorded.

Data analyses were performed with commercially available statistics software (SPSS version 12.0; SPSS Inc., Chicago, Illinois, USA). Chi-square analysis was used to test associations between categorical variables. A two-way repeated measures analysis of variance (ANOVA) was calculated to test for differences in the MFV of M_1 between the group that developed SVS and the group that did not develop SVS. A Mann-Whitney *U* test was used for non-normally distributed continuous variables. The significance level was set at $p < 0.05$. Receiver operating characteristic (ROC) curves were developed, and the area under the curve was calculated to evaluate the value of MFV of M_1 thresholds for predicting future SVS.

Results

Forty-five of the 98 patients with aneurysmal SAH were included in the present analysis. The most common reason for patient exclusion was the lack of adequate TCD windows. Among the 98 patients with aneurysmal SAH, 32 patients were excluded because of inadequate windows (representing 32.7% of all patients with aneurysmal SAH). The 45 patients who met all of the inclusion criteria were 13 men (28.9%) and 32 women (71.1%). The mean age was 61.9 $\pm$ 15.2 years.

SVS occurred in 11 of the 45 patients (24.4%). Arterial vasospasm was diagnosed with angiography in all of these patients. The median interval from SAH onset to the diagnosis of SVS was 7.36 days (range 2 to 12 days). Endovascular treatment for vasospasm was performed in 9 of 11 patients with SVS. Clinical characteristics of patients with and without SVS are compared in Table 1. No clinical or radiological variables were associated with SVS at admission.

TCD examinations performed on or before SAH day 14 were analyzed. MFV of M_1 in patients with

Table 1 Characteristics of patients with and without symptomatic vasospasm (SVS)

	Overall (n = 45)	No SVS (n = 34)	SVS (n = 11)	p Value
Demographics:				
Age (yrs)	61.9 ± 15.2	62.4 ± 16.5	60.3 ± 10.6	0.492
Male	13 (28.9%)	10 (29.4%)	3 (27.3%)	0.892
Admission clinical:				
Hunt and Hess grade				0.904
I	5	2	1	
II	17	14	2	
III	9	6	3	
IV	11	5	2	
V	3	1	1	
Admission radiological:				
Aneurysm location				0.728
ACoA	15	13	2	
distal ACA	6	4	2	
AChA	3	2	1	
PCoA	11	8	3	
MCA	8	5	3	
others	2	2	0	
Aneurysm treatment				0.838
clip	29	22	7	
coil	12	9	3	
clip and coil	2	1	1	
none	2	2	0	

ACA: anterior cerebral artery, AChA: anterior choroidal artery, ACoA: anterior communicating artery, MCA: middle cerebral artery, PCoA: posterior communicating artery.

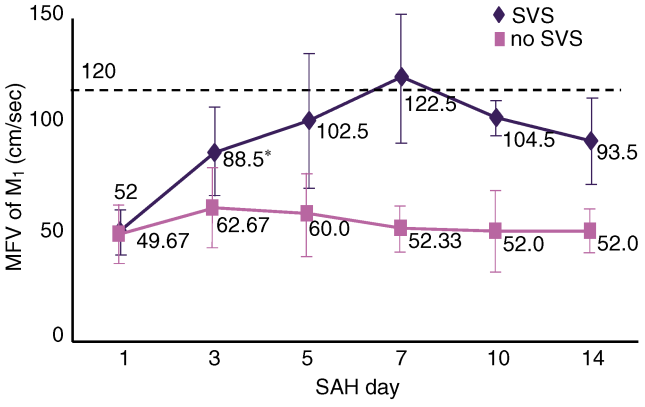

Fig. 1 Evolution of mean flow velocity (MFV) values in patients who did (*diamonds*) or did not (*squares*) develop symptomatic vasospasm (SVS) between subarachnoid hemorrhage (SAH) days 3 and 14. MFV of M_1 in patients with SVS increased progressively between SAH days 3 and 7, whereas MFV of M_1 in patients without SVS did not increase at any time. Two-way repeated measures analysis of variance showed significant differences in the progress of the MFV of M_1 between the SVS and no SVS groups ($p = 0.031$). The MFV of M_1 in the SVS group had already increased significantly on SAH day 3 compared with the no SVS group (*$p = 0.018$, Mann-Whitney *U* test).

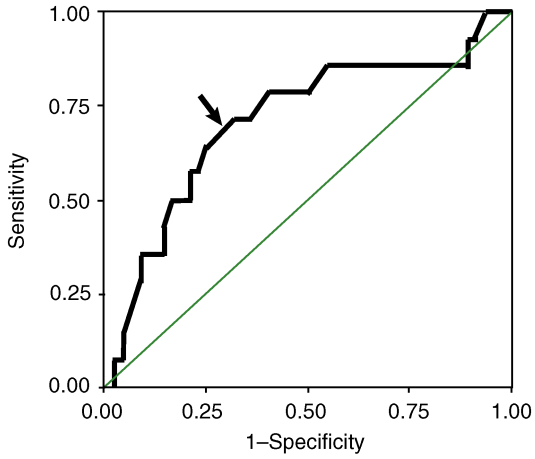

Fig. 2 Receiver operating characteristic (ROC) curve of mean flow velocity of M_1 on subarachnoid hemorrhage day 3 for the future occurrence of symptomatic vasospasm (SVS). The ROC curve analysis identified the optimal threshold value of 72.5 cm/sec (*arrow*) for predicting the future occurrence of SVS (sensitivity 71.4%, specificity 68.1%, and accuracy 82.3%). The area under the curve was 0.71.

SVS increased progressively between SAH days 3 and 7 before beginning to decrease, whereas MFV of M_1 in patients without SVS did not increase significantly at any time (Fig. 1). The highest MFV of M_1 in patients with SVS was found at SAH day 7. A two-way repeated measures ANOVA showed significant differences in the progress of the MFV of M_1 between the SVS group and the no SVS group ($p = 0.031$) (Fig. 1). The MFV of M_1 in the SVS group had already significantly increased on SAH day 3 compared with the no SVS group (Mann-Whitney *U* test, $p = 0.018$). The high values for the MFV of M_1 on SAH day 3 predict the future occurrence of SVS. The ROC curve showing the overall diagnostic utility of MFV of M_1 on the SAH day 3 for the future occurrence of SVS revealed an area under the curve of 0.71 (Fig. 2). The ROC curve analysis identified the optimal threshold value of 72.5 cm/sec for predicting the future occurrence of SVS. The threshold value has a global accuracy of 82.3%, with a sensitivity and specificity of 71.4% and 68.1%, respectively.

Discussion

In this study, we found that the TCD value in the early stage of SAH may be used to predict the future occurrence of SVS. We constructed a ROC curve to identify the flow velocities with the greatest sensitivity and specificity for predicting the SVS. The SVS group showed a higher MFV of M_1 than the no SVS group during the period on or after SAH day 3, and the threshold of 72.5 cm/sec MFV of M_1 on day 3 predicts the future occurrence of SVS. Thus, patients were more likely to suffer from SVS in the

Table 2 Summary of studies documenting the predictors of vasospasm

Author (Year)	Study type	No. of patients	Predictor for vasospasm	Diagnostic device/ material	Timing of examination	Main findings
Reilly et al. (2004)[22]	prospective observational	75	clot volume and clearance rate	CT	on admission	initial subarachnoid clot volume and the percentage of clot cleared per day predict SVS
Hirashima et al. (2005)[10]	retrospective	100	decrease in platelet count	serum	days 8–10 after SAH	ratio of the lowest platelet count and the admission count greater than 0.7 is a predictor of SVS
Udoetuk et al. (2007)[30]	retrospective	105	cerebral circulation time	DSA	within 24 hrs after SAH	prolonged CCT within 24 hrs after SAH is associated with subsequent angiographic vasospasm
Fountas et al. (2009)[8]	retrospective	41	CRP levels	serum and CSF	within 9 days after SAH	patients with angiographic vasospasm had higher CRP measurements in serum and CSF
Magge et al. (2010)[19]	retrospective	391	age	—	on admission	younger age is associated with increased incidence of angiographic vasospasm and SVS
Testai et al. (2011)[29]	prospective observational	25	circulating antiangiogenic factors	sEng and sFlt1	within 48 hrs after SAH	SVS patients had higher CSF sEng and sFlt1 levels within 48 hrs after SAH than no-SVS patients
Ibrahim and Macdonald (2012)[11]	prospective randomized	413	prolonged QT interval and tachycardia	ECG	within 48 hrs after SAH	ECG within 48 hrs after SAH predicts angiographic vasospasm, not associated with SVS
Wilson et al. (2012)[34]	retrospective	250	maximal SAH thickness	new scale using admission CT	on admission	new scale using admission CT predicts SVS
Budohoski et al. (2012)[3]	prospective observational	98	autoregulation index	TCD and NIRS	within 5 days after SAH	disturbed autoregulation in the first 5 days after SAH significantly increases the risk of DCI

CCT: cerebral circulation time, CRP: C-reactive protein, CSF: cerebrospinal fluid, CT: computed tomography, DCI: delayed cerebral ischemia, DSA: digital subtraction angiography, ECG: electrocardiography, sEng: soluble endoglin, sFlt1: soluble fms-like tyrosine kinase 1, NIRS: near-infrared spectroscopy, SAH: subarachnoid hemorrhage, SVS: symptomatic vasospasm, TCD: Transcranial Doppler.

future if the MFV of the M_1 on day 3 exceeded 72.5 cm/sec.

Previous studies have reported some risk factors that predict future SVS, such as high C-reactive protein value,[8] extended circulation time on angiography,[30] and decrease in platelet count.[10] Recent reports of predictors of vasospasm are shown in Table 2.[3,8,10,11,19,22,29,30,34] In addition, studies have used near-infrared spectroscopy, xenon CT, perfusion CT, and probability index, but many of these methods are detectors of vasospasm, not predictors of vasospasm. These reports showed no clear threshold. In contrast, the present report found a clear threshold for predicting vasospasm.

TCD spasm is often defined as a MFV of 120 cm/sec, and there is considerable support for this absolute value.[2] It is commonly used in the literature when examining the association with angiographic vasospasm or SVS. Recent studies have shown that a rise of the TCD level indicates the existence of angiographical vasospasm in ''the point of the time,''[13] and a MFV of 120 cm/sec indicates the existence of angiographical vasospasm regardless of the number of days from SAH onset.[20] However, among the patients with angiographical vasospasm, many do not develop SVS. Thus, prediction of SVS is exceedingly important.

No report has proved the relationship between the MFV of M_1 in the early stage of SAH and the future occurrence of SVS. The normal diameter of the MCA reported 2.9–3.4 mm,[25,31] and MFV is directly correlated with narrowing grade. Indeed, a statistically significant correlation was found between MFV and the angiographic lumen diameter of MCA, and MFV of 72.5 cm/sec indicated residual lumen diameter of the MCA of about 2.5 cm.[27] TCD examination has a high enough sensitivity to detect slight changes in the cerebral vessels. TCD may detect a slight narrowing of the vessel diameter due to the vasospasm. In future research, it is necessary to prove the vessel diameter change of a patient with a MFV of M_1 over 72.5 cm/sec on day 3 using magnetic resonance angiography or digital subtraction angiography. Age difference is known to exist in MFV measured by TCD. In this study, all age groups were statistically analyzed so that results could be generalized to any age group. An age-specific evaluation may allow a more detailed analysis.

Several important limitations of this study deserve emphasis. First, TCD was not performed in all patients with aneurysmal SAH. A lack of adequate TCD windows affected this study. The detection rate of adequate TCD windows was reportedly lower in African-American and Asian groups, and was also lower in older women.[15,16] Furthermore, distal type vasospasm presents difficulty in diagnosis by TCD. In these cases, false negative may occur due to a lack of strict accuracy of TCD value. It is necessary to compare sequential magnetic resonance angiography or CT angiography with TCD, and to examine the correlation to cover the weak point of TCD.

Second, the Lindegaard index (ratio of blood flow velocities in the MCA and internal carotid artery) could not be calculated because we did not routinely perform internal carotid artery MFV measurements. The Lindegaard index has been reported to predict SVS in small patient series.[14,17,20] Finally, patients with posterior circulation aneurysms were excluded from this study. However, those patients are not likely to suffer from SVS,[26] so the influence is small in this study.

Based on the results of this study, we determined a treatment strategy for vasospasm. In patients with a MFV of M_1 72.5 cm/sec or more on day 3, we intensified triple-H therapy (hypertension, hypervolemia, and hemodilution) and increased the number of TCD measurements. Furthermore, when we detected the rise of MFV, we performed angiography in an early stage of SAH within day 7 and performed the intra-arterial injection of fasudil hydrochloride, even if the patient was asymptomatic. We suggest that most cases of SVS may be prevented using this treatment strategy.

Increased MFV of M_1 during the early stage of SAH may predict the future occurrence of SVS. The threshold value that appears to be predictive of SVS is a MFV of M_1 72.5 cm/sec on SAH day 3. To prevent delayed cerebral ischemia, aggressive treatment for vasospasm is needed in patients with increased MFV during the early stage of SAH.

Conflicts of Interest Disclosure

We certify that there is no conflict of interest with any financial and personal relationships with other people or organizations regarding the material discussed in the manuscript. All authors have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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