Regional cerebral blood flow monitoring in the
diagnosis of delayed ischemia following aneurysmal
subarachnoid hemorrhage

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Object. The goal of this study was to evaluate regional cerebral blood flow (rCBF) monitoring, performed using thermal-diffusion (TD) flowmetry, as a novel means for the bedside diagnosis of symptomatic vasospasm.

Methods. Fourteen patients with high-grade subarachnoid hemorrhage (SAH) who underwent early clip placement for anterior circulation aneurysms were prospectively entered into the study. Thermal-diffusion microprobes were implanted into the white matter of vascular territories that were deemed at risk for developing symptomatic vasospasm. Data on arterial blood pressure, intracranial pressure, cerebral perfusion pressure, rCBF measurement obtained using a TD probe (TD-rCBF), cerebrovascular resistance (CVR), and blood flow velocities were collected at the patient’s bedside. The diagnosis of symptomatic vasospasm was based on the manifestation of a delayed ischemic neurological deficit and/or a reduced territorial level of CBF as assessed using stable Xe-enhanced computerized tomography (CT) scanning in combination with vasospasm demonstrated by angiography.

Bedside monitoring of TD-rCBF and CVR allowed the detection of symptomatic vasospasm. In the 10 patients with vasospasm the TD-rCBF decreased from 21 ± 4 to 9 ± 1 ml/100 g/min (mean ± standard error of the mean), whereas in the four other patients the TD-rCBF value remained unchanged (mean TD-rCBF = 25 ± 4 compared with 21 ± 4 ml/100 g/min). A comparison of the results of TD-rCBF and Xe-enhanced CT studies, as well as the calculation of sensitivities, specificities, predictive values, and likelihood ratios, identified a TD-rCBF value of 15 ml/100 g/min as a reliable cutoff for the diagnosis of symptomatic vasospasm. In addition, TD flowmetry was characterized by a more favorable diagnostic reliability than transcranial Doppler ultrasonography.

Conclusions. Thermal-diffusion flowmetry represents a promising method for the bedside monitoring of patients with SAH to detect symptomatic vasospasm. This is of major clinical interest for patients with high-grade SAH, who often cannot be assessed neurologically.

Key Words • cerebral blood flow • microcirculation • neuromonitoring • delayed ischemic neurological deficit • vasospasm

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ymptomatic vasospasm leading to delayed ischemia and neurological deterioration remains a primary cause of major incidences of morbidity and mortality following aneurysmal SAH. Although arterial narrowing of proximal intracranial vessels can be observed in up to 60 to 70% of patients with SAH, only 30% will experience a

DIND, which typically manifests between Days 5 and 14 post-SAH. At highest risk are patients who initially present with thick subarachnoid blood clots and a poor neurological condition.

Reliable and early detection of symptomatic vasospasm is critical for the treatment of patients with SAH. This especially applies to patients with high-grade SAH who are comatose or have to remain sedated, and thus are not amenable to neurological examination. Since its introduction,1 TCD ultrasonography has become widely accepted as an elegant, noninvasive, and inexpensive bedside method used to detect cerebral vasospasm. Recently, however, its specificity in detecting symptomatic vasospasm has been seriously questioned.2,26 As an alternative, several clinicians have demonstrated the usefulness of methods that allow direct assessment of the CBF status of the patient with SAH, specifically single-photon emission CT scanning, Xe imaging techniques, and positron emission tomography scanning.24 Nevertheless, adequate surveillance of patients with SAH remains hampered because these studies cannot be

Abbreviations used in this paper: ACA = anterior cerebral artery; ACoA = anterior communicating artery; CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CT = computerized tomography; CVR = cerebrovascular resistance; DIND = delayed ischemic neurological deficit; GOS = Glasgow Outcome Scale; ICA = internal carotid artery; ICP = intracranial pressure; MABP = mean arterial blood pressure; MCA = middle cerebral artery; rCBF = regional CBF; ROC = receiver operating characteristic; SAH = subarachnoid hemorrhage; SEM = standard error of the mean; sXe = stable xenon; sXe-rCBF = rCBF measured using sXe-enhanced CT; TCD = transcranial Doppler; TD = thermal-diffusion; TDF = TD flowmetry; TD-rCBF = rCBF measured using a TD microprobe; triple-H = hypertension, hypervolemia, hemodilution; WFNS = World Federation of Neurosurgical Societies.
performed at the patient’s bedside, only provide a snapshot view of CBF status, and are expensive as well as time consuming.

Recently, a novel TD microprobe was introduced for the continuous bedside monitoring of rCBF (TD-rCBF values in ml/100 g/min). Our previous experimental and clinical studies have demonstrated that this method allows us to detect even discrete changes in CBF reliably.21-24,25 Furthermore, the TD-rCBF values have been validated using the Xe-enhanced CT technique.25 As a consequence, TDF may be a promising technique to overcome obstacles faced in the reliable detection of symptomatic vasospasm at the patient’s bedside.

In this report, we demonstrate that TDF allows the assessment of cerebral hemodynamic parameters, such as perfusion and vascular resistance, in patients with SAH and reliably detects the development of vasospasm-associated hypoperfusion. Furthermore, we determine the diagnostic cutoff values, predictive values, and likelihood ratios of TDF for identification of symptomatic vasospasm. Finally, we analyze whether multifocal rCBF monitoring increases diagnostic sensitivity in the identification of symptomatic vasospasm when compared with the use of a single probe.

Clinical Material and Methods

Study Population and Treatment

The study was approved by the local research ethics committee and institutional review board. Fourteen patients with aneurysmal SAH were prospectively enrolled. Inclusion criteria were the following: 18 to 70 years of age; severe SAH with a thick subarachnoid blood clot observed on CT scanning (that is, Grade III–V according to the WFNS classification1 and Grade 3 according to the Fisher scale5); confirmation of a ruptured anterior circulation saccular aneurysm by cerebral angiography and surgery; uneventful surgical clip occlusion of the aneurysm within 48 hours following rupture; and informed consent obtained from the patient or the closest relative. External ventricular drainage was established in all patients. Routine monitoring of patients included invasive measurement of MABP, central venous pressure, and ICP. Cerebral perfusion pressure was calculated as CPP = MABP − ICP. Intracranial pressure elevations (>20 mm Hg) were treated according to standardized guidelines. Patients who were comatose or had to be sedated due to an elevated ICP remained intubated and artificially ventilated. The MABP was kept between 80 and 100 mm Hg, and moderate volume expansion was administered to maintain a central venous pressure of 5 to 8 cm H2O and a hematocrit of approximately 35%. Hypertension therapy and volume expansion were initiated if the development of vasospasm was suspected based on clinical, TCD, or radiographic examinations. In contrast, therapeutic decisions were not based on the results of TDF.

Thermal-Diffusion Flowmetry

Following clipping of the aneurysm, two TD microprobes (Hemedex, Inc., Cambridge, MA) were implanted into the vascular territories deemed at highest risk for developing vasospasm-associated hypoperfusion. Consequently, in the case of an ICA or MCA aneurysm, the probes were implanted into the ipsilateral MCA and ACA territories, whereas in the case of an ACoA aneurysm, the probes were implanted into both ACA territories. For implantation of the probes, a one-way bolt (DID Medical, Simbach/Inn, Germany) was inserted through a 3.2-mm coronal burr hole placed 20 mm (for placement in the ACA territory) or 60 mm (for placement in the MCA territory) lateral to the midline. The probes were inserted through the bolt, placed subcortically at a depth of 20 to 25 mm below the level of the dura mater (that is, in the white matter), and secured by tightening the bolt. Measurements of TD-rCBF were performed at a sampling rate of 1 Hz by using a perfusion monitoring system (model TDP200; Hemedex, Inc.). For interpretation of the focal TD-rCBF data, it is important to note that in white matter the CBF is expected to range between 18 and 25 ml/100 g/min, compared with the mean global CBF, which is expected to range between 40 and 50 ml/100 g/min.6 In addition, the CVR was calculated as $\text{CVR} = \frac{\text{TD-rCBF}}{\text{CPP}}$.23 By considering the individual CPP necessary to achieve a certain cerebral perfusion, the CVR may provide complementary bedside information on the severity of the vasospasm. Furthermore, calculation of the CVR would correct for a varying CPP when TD-rCBF values are compared intra- or interindividually.

Transcranial Doppler Ultrasonography

Blood flow velocities were assessed bilaterally by using a 2-MHz transducer over the temporal bone window. The sampling depth was selected by the investigator by using a range-gated technique. First, variable transduction depths and anatomical criteria were used to locate the bifurcation of the ICA, followed by the identification of the MCA. In addition, the extracranial portion of the ICA was assessed and the Lindegaard ratio (or index)12 was calculated as the ratio of MCA velocity to ipsilateral extracranial ICA velocity. Flow velocities greater than 120 cm/second, a Lindegaard index greater than 3, or an increase in the flow velocity by more than 50 cm/second within 24 hours were regarded to be pathological.

Stable Xe-Enhanced CT Scanning

The sXe-enhanced CT scanning method represents an accepted method to obtain clinical and quantitative rCBF measurements (sXe-rCBF).7,27 For determination of sXe-rCBF values, a 4.5-min wash-in protocol was applied. Patients received a mixture of medical-grade 30% sXe, 60% O2, and balanced air, while a three-level investigation (slice thickness 10 mm) was performed. The end-tidal CO2 level was adjusted to approximately 35 mm Hg. Patients breathed the Xe/O2/air mixture for 4.5 minutes after two baseline scans had been obtained. During this period, six enhanced scans were acquired. The sXe-enhanced CT results were used in two different ways. For the assessment of the hemodynamic relevance of vasospasm, territorial rCBF was calculated for the bilateral MCA and ACA territories (sXe-rCBF). In contrast, for validation of the TD microprobes at the beginning of each monitoring period, focal CBF was evaluated by placing a circular region of interest of 500 voxels (~5 cm2, 1 voxel = 1 × 1 × 10 mm3) around the artifact of the microprobe tip.25
Monitoring of CBF in patients with SAH

Cerebral Angiography

Standard cerebral panangiography was performed using a digital subtraction method. Angiographically confirmed vasospasm was defined as any moderate-to-severe (that is, > 30%) narrowing of the diameter of the arterial vessel lumen on high-resolution images.

Study Protocol

Following surgical clip placement and probe implantation, a CT scan and an sXe-enhanced CT study were obtained in all patients on postoperative Day 1. Thereby, acute ischemic lesions were identified and baseline sXe-rCBF values were obtained. During the subsequent monitoring period, data on MABP, ICP, CPP, TD-rCBF, CVR, and blood flow velocities were collected at the bedside every 12 hours. According to the time course of vasospasm, a second sXe-enhanced CT study, followed by a control angiogram, was obtained between Days 7 and 9 post-SAH, or earlier in cases in which there was neurological deterioration or pathological TCD values. As soon as the diagnostic workup for symptomatic vasospasm had been completed, therapy was individualized to the patient’s pathological condition.

Definition of Symptomatic Vasospasm

In awake patients, that is, neurologically assessable patients, symptomatic vasospasm was defined as a DIND combined with angiographically verified vasospasm. Because most patients in this study were comatose or sedated, however, the definition of symptomatic vasospasm was based on findings of the second sXe-enhanced CT study, as reported previously.3,7 Thus, symptomatic vasospasm was present if the mean sXe-rCBF value was less than 32 ml/100 g/min in the presence of angiographically verified vasospasm, indicating hemodynamically relevant vasospasm.

Statistical Analysis

Patient characteristics and monitoring parameters are given as mean values ± standard deviation and mean values ± SEM, respectively. The mean values were calculated from the daily average in each patient. Comparisons of dependent and independent variables were tested by applying analysis of variance followed by paired and unpaired Student t-tests and Bonferroni probabilities. Probability values less than 0.05 and less than 0.01 were considered to be significant and highly significant, respectively. The correlation between TD-rCBF and sXe-rCBF values was assessed by univariate linear regression analysis.

To determine diagnostic cutoff values for TDF to identify symptomatic vasospasm, first complex and then two-by-two contingency tables with multiple cutoffs were generated to calculate the sensitivity, specificity, and positive and negative predictive values, as well as the likelihood ratios for negative and positive results.19

To compare the diagnostic value of TDF to TCD ultrasonography, ROC curves were generated for values of TD-rCBF, CVR, and blood velocity, either alone or in combination with the Lindegaard index. Therefore, pairs of true-positive and false-positive rates corresponding to each possible diagnostic threshold of the individual diagnostic tests were plotted onto a graph for a visual comparison.39

Results

Patient Characteristics

The mean age of our study population was 50 ± 12 years (range 21–69 years). All aneurysms were located within the anterior circulation (ICA in four patients, ACoA in eight, and MCA in two). The mean baseline sXe-rCBF was 44 ± 11 ml/100 g/min. Patients were monitored for a time period of 7 ± 2 days. There were no complications related to probe implantation or to monitoring TD-rCBF values. A favorable outcome according to the GOS® (Scores 4 and 5) was achieved in 36% of patients.

In 10 patients with vasospasm, the diagnosis of symptomatic vasospasm was established based on the development of a DIND (two patients) or demonstration of hemodynamically relevant vasospasm (eight patients). In this group, the mean sXe-rCBF value at the time of diagnosis was 27 ± 2 ml/100 g/min, which was significantly lower than that measured in the four patients without symptomatic vasospasm (sXe-rCBF = 48 ± 3 ml/100 g/min; p < 0.05). Ischemic lesions (four complete territorial and three incomplete territorial) developed in seven patients with vasospasm, despite the fact that they were given aggressive triple-H therapy. In contrast, no ischemic lesions were identified on CT scans obtained in patients without vasospasm at discharge from the hospital.

Direct Assessment of Cerebral Hemodynamics by Using TD

Figure 1 demonstrates how TDF complemented other bedside methods of monitoring in our population of patients with SAH. Although both TCD ultrasonography and CPP monitoring obtained only indirect and unreliable measurements of cerebral perfusion (Fig. 1A and B), TDF enabled a direct assessment of cerebral hemodynamic parameters (Fig. 1C). Following an early period of posthemorrhage hypoperfusion (TD-rCBF 18 ± 1 ml/100 g/min), the TD-rCBF recovered to 23 ± 2 ml/100 g/min on Days 2 and 3 post-SAH, and finally decreased steadily from Day 4 to Day 9 (TD-rCBF = 13 ± 1 ml/100 g/min), as expected for a patient population with severe SAH. The TD-rCBF decreased despite an elevation in CPP (from 86 ± 4 mm Hg to 102 ± 3 mm Hg), reflecting the severity of the vasospasm and the resistance to therapy on the part of many of these patients. This relationship between perfusion pressure and blood flow was summarized by calculating the CVR, which reflected the severity of the vasospasm (Fig. 1D).
Thermal-Diffusion Flowmetry Detection of Vasospasm-Associated Hypoperfusion

The bedside monitoring of TD-rCBF and CVR confirmed symptomatic vasospasm in patients presenting with a DIND and detected symptomatic vasospasm in comatose patients. This is illustrated by the following two case reports.

Case 1. This 44-year-old woman presented with a WFNS Grade III SAH. Cerebral angiography revealed a right ICA aneurysm originating at the level of the posterior communicating artery. This aneurysm was surgically clipped 19 hours post-SAH. Thermal-diffusion microprobes were implanted into the right MCA and right ACA vascular territories. On Day 3 post-SAH, the patient was extubated and assigned a Glasgow Coma Scale score of 13 to 14 points. At that time she displayed no neurological deficits. On Day 4 post-SAH, for the first time the patient presented with a left hemiparesis. In parallel, blood flow velocities in the right ICA and MCA had increased to 137 cm/second. Control angiography was performed the same day and demonstrated moderate-to-severe vasospasm in the right M1 and A1 segments. Following initiation of aggressive triple-H therapy the patient’s hemiparesis gradually improved. A control CT scan obtained at discharge revealed disseminated minor hypodensities within the right MCA vascular territory. At discharge, the patient was classified as having made a good recovery (GOS Score 5).

The analysis of TD-rCBF and CVR during the 7-day monitoring period demonstrated that within the right MCA territory the TD-rCBF had already started to decline on Day 3 post-SAH, reaching its lowest value on Day 4 (4 ml/100 g/min), when the patient first displayed her neurological deficit (Fig. 2). At that time, only a high CPP could maintain the minimal perfusion, which was reflected in the high values of CVR (Fig. 2).
CVR on Day 4. During the following days, in parallel to the clinical improvement of the patient, the TD-rCBF within the right MCA territory gradually recovered, which was not only attributable to the triple-H therapy, but also to the reversal of vasospasm as indicated by normalization of the CVR. At the same time the TD-rCBF and CVR within the right ACA territory were unaffected.

**Case 2.** This 49-year-old woman presented with a WFNS Grade V SAH. Cerebral angiography revealed a small ACoA aneurysm that was surgically occluded 15 hours post-SAH (Fig. 3A). The patient’s baseline sXe-rCBF values were 55 and 59 ml/100 g/min (Fig. 3C). Thermal-diffusion microprobes were implanted into the ACA vascular territories. Postoperatively, the patient had to remain sedated because of brain swelling and ICP elevations. During the whole treatment period, blood flow velocities were lower than 120 cm/second. On Day 7 post-SAH, we unexpectedly found severe bilateral hypoperfusion on sXe-enhanced CT images (sXe-rCBF = 25 and 28 ml/100 g/min), and cerebral angiography confirmed the diagnosis of symptomatic vasospasm in the A1, A2, and M1 segments (Fig. 3B and D). Three weeks later, the patient experienced hydrocephalus, which necessitated implantation of a ventriculoperitoneal shunt. At discharge, the patient was classified as having made an unfavorable recovery (GOS Score 3).

**Diagnosis of Regional Hemodynamic Vasospasm**

We next sought to determine diagnostic cutoff values for TD-rCBF and CVR that would be indicative of symptomatic vasospasm within the monitored vascular territory. Because such a diagnostic threshold value already exists for the sXe-enhanced CT method (that is, a territorial sXe-rCBF < 32 ml/100 g/min), we first compared sXe-rCBF measurements obtained on the day of the diagnostic workup for vasospasm with the TD-rCBF measurements obtained on the same day (Fig. 6). The regression analysis of this comparison suggested a TD-rCBF cutoff value between 10 ml/100 g/min and 15 ml/100 g/min. Similarly, a comparison between the CVR and corresponding sXe-enhanced CT measurements revealed a CVR cutoff value between 10 and 12 for the diagnosis of symptomatic vasospasm (data not shown).

To compare the diagnostic value of these cutoff values with those of TCD ultrasonography more fully, ROC curves were generated for TD-rCBF, CVR, and blood velocity values, either alone or in combination with the Lindegaard index (Fig. 7). With reference to the graphic representation in Fig. 7, the upper left-hand corner of the plot denotes the perfect diagnostic test, which is characterized by a true-positive rate of 1 and a false-positive rate of 0. Consequently, the point on an ROC curve that is closest to this upper left-
alone or in combination with the Lindegaard ratio or index (TCD and blood flow velocities obtained using TCD ultrasonography were plotted. Each possible diagnostic threshold of the individual diagnostic test LI). Pairs of true-positive and false-positive rates corresponding to every vascular territory at highest risk, in which case one patient with symptomatic vasospasm would have been missed the vascular territory at highest risk, in which case one patient with symptomatic vasospasm would have been missed at all. Using TDF, symptomatic vasospasm was already indicated 3 ± 2 days earlier than by conventional means. 

Discussion

The results of this study confirm the feasibility of using TDF monitoring of rCBF to determine the presence of symptomatic vasospasm in patients with SAH. Despite the minimal invasiveness of the method, both the implantation of the microprobes as well as the monitoring procedure have proved to be safe in a population of patients with high-grade SAH. In addition to the quantitative assessment of rCBF, we have introduced an additional parameter that can be assessed by TDF, namely CVR, which provides complementary bedside information on vasospasm severity by considering the CPP necessary to achieve a certain perfusion. Finally, our results and those of the statistical analysis demonstrate that both rCBF and CVR monitoring detect symptomatic vasospasm with a higher reliability than TCD ultrasonography.

The diagnosis of symptomatic or hemodynamically relevant vasospasm remains a problem in the treatment of patients with SAH. Cerebral angiography is still the gold standard in the diagnosis of cerebral vasospasm. The specificity for angiography in the diagnosis of symptomatic vasospasm, however, has recently been calculated to be 50%, which indicates that if the patient cannot be assessed neuroradiologically, the hemodynamic relevance of angiographic vasospasm remains obscure. In these situations, elevated blood flow velocities unfortunately fail to improve diagnostic safety, because they do not correlate with cerebral perfusion and lack a sufficient specificity for the reliable confirmation of symptomatic vasospasm. This is why clinicians have long sought to assess CBF in patients with SAH directly. So far, three diagnostic modalities have gained widespread acceptance: single-photon emission CT, Sxenhanced CT, and positron emission tomography scanning. All three methods have clearly demonstrated that, especially in patients with high-grade SAH, a direct assessment of CBF is valuable to confirm symptomatic vasospasm and to treat it adequately. Nevertheless, it has al-

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<th>Cutoff Value</th>
<th>Sensitivity</th>
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<th>PPV</th>
<th>NPV</th>
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<th>LR−</th>
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<td>&lt;10 ml/100 g/min</td>
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* LR+ = likelihood ratio for a positive test result; LR− = likelihood ratio for a negative test result; ND = not determined; NPV = negative predictive value; PPV = positive predictive value.

Identifying the Patient With Symptomatic Vasospasm

When a TD-rCBF cutoff value of 15 ml/100 g/min was applied to the two microprobes implanted in the vascular territories at risk, none of the patients with symptomatic vasospasm were missed by TDF (sensitivity 100%; specificity 50%). Interestingly, this result would have been only slightly worse if only one probe had been implanted into the vascular territory at highest risk, in which case one patient with symptomatic vasospasm would have been missed (sensitivity 90%; specificity 75%). Nevertheless, in comparison with the results obtained using TCD criteria (sensitivity 80%; specificity 50%), both unifocal and multifocal TD-rCBF monitoring provided a more favorable diagnostic reliability. With respect to timing, pathological TD-rCBF values preceded the diagnosis of symptomatic vasospasm in all patients. Using TDF, symptomatic vasospasm was already indicated 3 ± 2 days earlier than by conventional means.
Monitoring of CBF in patients with SAH

so become apparent that these modalities share significant drawbacks, because CBF studies cannot be routinely performed at the patient’s bedside and only provide a snapshot view of flow. Similarly, indicator methods that are applicable at the bedside represent discontinuous processes that permit repeated examinations only at 30- to 60-minute intervals, at best, and often necessitate the use of radioactive and expensive tracers (for example, $^{133}$Xe inhalation and injection methods).

Consequently, the ability to assess rCBF at the patient’s bedside repeatedly or continuously makes TDF an appealing adjunctive diagnostic tool in the monitoring of patients with SAH. Carter and coworkers were the first to demonstrate the feasibility of long-term TDF in patients with SAH by using a cortical surface probe. In the present study we have used a TDF system in which the size of the probe has been reduced to less than 1 mm and rCBF measurements have become more stable as well as more reliable. We implanted the microprobes at a depth of 20 to 25 mm below the level of the dura mater (that is, in the white matter) for two reasons. First, only an implantation depth greater than 10 mm below the cortical surface provides the thermal stability that is necessary to obtain stable perfusion measurements while applying TD principles. Second, the same implantation site is currently used for standard neuromonitoring of oxygenation and metabolic parameters.

Both TD-rCBF and CVR values demonstrated distinct courses in patients with and without vasospasm, and matched the results of our clinical and radiographic examinations. Low TD-rCBF and high CVR values were predominantly observed in patients presenting with a DIND and/or a significant reduction in cerebral perfusion status. Importantly, differences in TD-rCBF and CVR values between patients with and without vasospasm became apparent days before a conventional diagnosis of symptomatic vasospasm, suggesting that TDF may allow us to identify patients at risk of developing a DIND prospectively.

Besides the observation that TDF is able to detect a low flow state in patients with vasospasm, we have also provided cutoff values for the diagnosis of symptomatic vasospasm within the vascular territory under surveillance. According to the ROC curves, a TD-rCBF value of 10 ml/100 g/min and a CVR value of 10 may represent the best diagnostic thresholds, because they minimize the sum of false-positive and false-negative rates. It should be noted, however, that an interpretation of these ROC curves also has to consider the individual patient’s needs and the consequences of missing the correct diagnosis. In patients suffering from symptomatic vasospasm, false-negative misses are highly dangerous and should be minimized, if necessary at the cost of increasing the false-positive rate. Based on these concerns, we suggest that the diagnostic threshold that maximized the true-positive rate (15 ml/100 g/min) should be picked. This algorithm, however, will leave a diagnostic gray zone between a TD-rCBF of 10 ml/100 g/min and that of 15 ml/100 g/min. In this case, the additional calculation of the CVR becomes of special interest in the identification of those patients who are dependent on a high CPP to achieve this borderline perfusion and thus suffer from symptomatic vasospasm. Of course, all positive results obtained using TDF should be rapidly followed up by obtaining an angiographic study to confirm the diagnosis and to initiate endovascular therapy if indicated.

Compared with traditional CBF thresholds (normal range 40–55 ml/100 g/min, loss of neuron function at 20 ml/100 g/min, failure of neuron integrity at 10 ml/100 g/min), the TD-rCBF values obtained in this study appear to be relatively low. In part, this discrepancy can be explained by our implantation protocol, in which TD-rCBF values were assessed within the white matter, that is, where physiological flow ranges between 18 and 25 ml/100 g/min. This is why our results are applicable only to TD-rCBF measurements that follow the protocol outlined in this study. A potential second explanation for the low TD-rCBF values may be the fact that, following a high-grade SAH, CBF is depressed per se, which has been attributed to reduced cerebral metabolism.

The major limitation of current monitoring strategies, which include not only TDF but also brain tissue oxygen measurements and microdialysis, is the focal character of the techniques, mandating a proper implantation of the microprobe into the vascular territory that is deemed to be at highest risk for developing vasospasm. Nevertheless, a considerable risk of missing a patient with symptomatic vasospasm remains and has been recently reported to be approximately 20% in the case of microdialysis. Therefore, it has been repeatedly discussed whether implantation of multiple probes may minimize the risk of monitoring only unaffected tissue. For this reason, we implanted two TD microprobes into distinct vascular territories and calculated sensitivities and specificities for identifying a patient with symptomatic vasospasm. Unfortunately, the number of patients with SAH in this study population is too small to allow final conclusions; however, our data indicate that implantation of multiple probes carries only minor benefits when compared with a proper unifocal monitoring approach.

Based on the results of this study we suggest that physicians incorporate bedside TD-rCBF measurements into future paradigms of vasospasm management. This will provide assistance in the early detection of delayed cerebral ischemia and in monitoring the efficacy of therapeutic interventions that aim at improving cerebral hyperperfusion. Despite the superior diagnostic reliability of TDF, we would not suggest that TCD ultrasonography be discarded from the paradigms of vasospasm management at the current stage. First, elevated blood flow velocities (together with the CVR) may aid decision making when TD-rCBF values range within the diagnostic gray zone. Second, TCD ultrasonography may be beneficial in the rare case in which vasospasm develops within a vascular territory that is not under TD-rCBF surveillance.

Conclusions

In conclusion, TDF represents a promising method of continuous bedside monitoring of patients with SAH to detect symptomatic vasospasm. This is of major interest for patients with SAH who cannot be assessed clinically, that is, those who have suffered a severe hemorrhage, remain comatose, or have to remain sedated to control intracranial hypertension. The limiting character of the focal nature of rCBF measurements can be largely overcome by careful selection of the vascular territory to be monitored and following a standardized implantation protocol. In a next step, the
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