Cerebral infarction with permanent vasospasm-induced delayed ischemic neurological deficits (DIND) after aneurysmal subarachnoid hemorrhage (aSAH) is a feared and unfortunately frequent complication, responsible for poor functional and overall outcome. The pathophysiology of DIND and vasospasm-induced delayed cerebral infarction (DCI) after aSAH is multifactorial and still not fully understood. It is well accepted that vasospasm is a major contributor to DIND and DCI, but it is also assumed that processes already initiated shortly after aSAH render some brain areas more vulnerable for vasospasm than others. In up to 15% of patients, cerebral infarction and a fixed neurological deficit (including death) are irreversible end points of a dynamic process starting with tissue predisposition and asymptomatic vasospasm, followed by symptomatic vasospasm and transient DIND. For the successful prevention of infarction by antivasospastic therapy, timely recognition of...
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A total of 43 patients with aSAH, who were admitted between August 2012 and December 2013, were enrolled in this prospective single-center study. The local institutional review board approved the study protocol. Patients who were younger than 18 years, pregnant, had severe renal dysfunction, or admitted later than 24 hours after bleeding were excluded. All patients were treated according to the institute’s standard protocol for management of patients with aSAH. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

The diagnosis of aSAH was confirmed by a CT scan and CT angiography (CTA) and/or DSA. The aneurysm was either clipped or coiled within 48 hours after bleeding. All patients were kept at the intensive care unit between Day 0 and at least Day 14 post-aSAH. Blood flow velocity (BFV) was routinely measured using TCD on a daily basis, starting with the day of admission. A mean BFV > 120 cm/sec was defined as TCD-confirmed vasospasm. DIND was defined as new neurological deterioration (e.g., aphasia, hemiparesis, confusion, consciousness alteration, and so on) after exclusion of hydrocephalus, rebleeding, seizures, and metabolic disturbances. Routine CT scans were performed in every patient within 1 day after aneurysm treatment to rule out treatment-induced ischemia and on Day 10 after bleeding. In patients who underwent aneurysm clipping, CTA was additionally obtained with the first postoperative native CT scan (i.e., without application of contrast media). DCI was defined as hypodensity on CT scan, which was not visible on the posttreatment CT scan and after excluding other causes. All patients received intravenous nimodipine for 14 days. Normovolemia was maintained in patients without TCD-vasospasm. In any patient with TCD-vasospasm, noradrenaline was used to induce arterial hypertension (target systolic blood pressure 160–180 mm Hg). Some patients with symptomatic vasospasm and CTP-proven perfusion deficits in the corresponding vessel territory, despite maximal conservative antivasospastic treatment, underwent either intraarterial application of nimodipine, balloon dilation, or a combination of both.

Use of the CTP Study

The CTP Algorithm

Investigation with CTP was routinely performed in all patients in the acute phase (Days 3–5) after aSAH. In cases of rapidly progressive TCD-vasospasm (BFV increase > 50 cm/sec within 24 hours), CTP was repeated. Additionally, patients who were comatose and/or sedated were routinely investigated with CTP on Day 7 after aSAH. Thus, noncomatose and/or nonsedated patients without TCD-vasospasm were imaged once, those with TCD-vasospasm at least twice; comatose and/or sedated patients without TCD-vasospasm were imaged twice, and those with TCD-vasospasm at least 3 times.

Imaging Protocol

All images were obtained on a 128-slice multidetector CT scanner (Siemens Definition AS+; Siemens Healthcare Sector). The following parameters were used for nonenhanced spiral neuro mode scan, covering skull base and the cerebrum with a caudal-cranial range of 12 cm: 120 kV, 450 mAs, rotation time 1.0 second, maximum pitch 0.8, slice collimation 50 × 0.6 mm, kernel H31f, 512 matrix. Routine axial and coronal maximum-projection reconstructions were made, with a 5-mm slice thickness and a 1-mm interslice distance.

The CTP data were acquired using a periodic spiral approach (adaptive 4-dimensional spiral mode) of 30 pe-
Data Analysis

Two experienced neuroradiologists (P.S. and K.D.), who were blinded to all clinical data and the clinical course, assessed the CTP and CTA images. 3D perfusion parameter maps were used to show the distribution of hypoperfusion. Readers were asked to assess the presence of a focal hypoperfused area (defined as a visual abnormality) on any of the parameter maps consisting of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), time to start (TTS), time to peak (TTP), and time to drain (TTD). If hypoperfusion was present, readers had to assign it to one of the vascular territories. Perfusion abnormalities that persisted on the basis of a primary hemorrhagic event, previous ischemia, or surgical intervention were excluded as acute perfusion deficits. Consensus judgment was determined after reviewing the images independently.

Axial and coronal CTA reconstructions were used to identify vasospasm or occlusion in the following vessels: proximal anterior cerebral artery (A1), middle cerebral artery (M1/M2), and the posterior cerebral artery (P). In cases with additional DSA, DSA was also used to spot vessel abnormalities. By definition, cerebral vasospasm is a focal narrowing of vessel diameter compared with the same segment in the initial CTA at the time of SAH. A vessel narrowing < 50% was considered as mild, 50%–75% as moderate, and > 75% as high-grade angiographic vasospasm.

In all patients, CTP parameter maps were used to make treatment decisions. Patients with symptoms of vasospasm, increased BFV in TCD, abnormal CTP data (defined as highly visual abnormality on the parameter maps in more than one-third of 1 or more vascular territories), and arterial vasospasm on single-phase CTA axial and coronal MIP reconstructions underwent DSA, with the possibility to perform endovascular treatment. The perfusion deficits were divided into 2 main groups of territorial and nonterritorial. Territorial perfusion deficits were diagnosed if the perfusion deficit was confined to a vessel territory (Fig. 1A). Nonterritorial perfusion deficits were diffuse deficits, including multiple vessel territories or the watershed area between 2 vessel territories (Fig. 1B).

Statistical Analysis

Fisher’s exact test was used to evaluate the sensitivity and specificity of perfusion deficits on CTP for the identification of patients at risk for developing DIND and tissue at risk for DCI, respectively. We used a paired t-test to assess the correlation between perfusion deficit on the CTP and DIND/DCI.

Results

A total of 43 patients were included in the study. The mean age of patients was 52.0 (29–82) years. Thirty patients were women and 13 were men. In all patients, aSAH was diagnosed within 24 hours after symptom onset, which was considered the moment of aneurysm rupture. Patients with history of minor leak and patients with ill-defined symptom onset were excluded. Multiple aneurysms were identified in 14 patients. By dichotomizing the Hunt and Hess grade into good (Grades I–III) and poor (Grades IV and V), we found a good Hunt and Hess grade in 23 of the 43 patients (53%). Thirty-nine of the 43 patients (91%) had a Fisher Grade 3 or 4 on the initial CT scan. The ruptured aneurysm was clipped in 25 patients and coiled in 18 patients. The posttreatment CT scan showed partial cerebellar infarction in 2 patients with clipped basilar artery aneurysm and infarction of the recurrent artery of Heubner in 1 patient with clipped anterior communicating artery aneurysm. The CT scan ruled out spatula-induced hypodensity/contusion in the frontal and temporal lobes in all clipped aneurysms. There was neither vasospasm in the post surgery CTA, which was performed with the native CT, nor in the final angiographic series after completion of coiling. A summary of patient characteristics is given in Table 1.

Incidence of DIND and DCI in the Study Population

Delayed ischemic neurological deficits occurred in 13 of the 43 patients (30%) within 2 weeks after aSAH, of whom 7 patients (54%) had a transient and 6 patients (46%) a permanent DIND. Vasospasm-associated DCI developed in 11 of the 43 patients (26%).

Early CTP (on Days 3–5) for Identification of Patients at Risk for DIND and of Tissue at Risk for DCI

In 39 of 43 patients (91%), early CTP was done on Day 3 after aSAH, in 1 patient (2%) on Day 4, and in 3 patients on Day 5 (7%); a delay of imaging beyond Day 3 occurred because of a nonfunctioning CT scanner. Perfusion deficits in CTP on Days 3–5 were seen in 14 of the 43 patients (33%), of whom 10 (72%) developed DIND (in 4 of these 10 patients, DIND occurred on Days 3–5 and in 6 patients (46)) performed DSA, with the possibility to perform endovascular treatment.
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on Days 5–14 after aSAH). Seven of the 10 patients (70%) with early perfusion deficits and DIND had territorial deficits and 3 patients (30%) had nonterritorial deficits.

The remaining 4 patients (28%) with early perfusion deficits (but without DIND) had nonterritorial perfusion deficits. Three patients (21%) developed DCI without preceding DIND, and 1 patient (7%) had neither DIND nor DCI. Three patients without early perfusion deficits in CTP later developed DIND; in these patients, a second CTP after Day 5 documented territorial perfusion deficits.

Delayed cerebral infarction occurred in 9 of the 14 patients (64%) with early perfusion deficits, of whom 6 patients (67%) had preceding DIND. In the remaining 3 patients (33%), DCI occurred without DIND. Two additional patients developed DCI, but did not demonstrate early perfusion deficits on CTP nor did they have preceding DIND.

The sensitivity and specificity of perfusion deficits on early CTP for the identification of patients at risk for developing DIND was 77% (95% CI 46%–95%) and 87% (95% CI 69%–96%), respectively, with a statistically significant correlation between early perfusion deficits on the CTP and the occurrence of DIND after aSAH (Pearson r = 0.62, 95% CI 40%–79%, p < 0.0001). The positive predictive value (PPV) was 71% (95% CI 42%–92%) and the negative predictive value (NPV) was 90% (95% CI 73%–98%) (Fig. 2A).

**FIG. 1.** Whole-brain CTP with perfusion deficits in the middle cerebral artery territory on the right side (A) and diffuse unspecific deficits (B). Figure is available in color online only.
Early CTP identified tissue at risk for developing vasospasm-associated DCI with a sensitivity of 82% (95% CI 8%–98%) and a specificity of 84% (95% CI 67%–95%), respectively, and the PPV and NPV were 33% (95% CI 9%–90%) and 60% (95% CI 15%–100%), respectively. The sensitivity and specificity of CTP in rapidly progressive TCD-vasospasm for identification of tissue at risk were 100% (95% CI 15%–100%) and 83% (95% CI 35%–99%), respectively, and the PPV and NPV were 67% (95% CI 9%–99%) and 100% (95% CI 47%–100%), respectively.

Use of CTP on Day 7 in Patients Who Were Comatose and/or Sedated

Seven of the 43 patients (16%) who were comatose and/or sedated on Day 7 after the initial bleeding received an additional CTP on Day 7. Four of these 7 patients (57%) had perfusion deficits on the CTP on Day 7, of whom 3 patients had nonterritorial and 1 patient had a territorial perfusion deficit. All 4 patients with perfusion deficits developed DCI. None of the 3 patients without perfusion deficits developed DCI.

Discussion

CT perfusion is a well-established tool in the imaging of ischemic stroke. Thus, it is not surprising that CTP was also used in the diagnostic workup after aSAH, with the aim to detect impending vasospastic infarction during the so-called vasospasm period between Days 5 and 14 after the initial bleeding. Wintermark et al. performed a retrospective analysis of 27 patients with aSAH who were suspected to develop angiographic vasospasm and therefore underwent CTP/CTA, TCD, and DSA between Days 6 and 8 after the initial bleeding. They found a significant correlation of CTP/CTA findings with those of DSA. The most accurate CTP parameter (based on ROI analysis) in this study for the detection of angiographic vasospasm was MTT, with a cutoff at 6.4 seconds and a very high NPV of 98.7%. Sanelli et al. performed a retrospective analysis of a single ROI-based CTP in 75 patients between Day 0 and Day 3 after aSAH and found a statistically significant reduction of CBF and prolongation of MTT on early CTP in patients who develop angiographic vasospasm later. In a second retrospective study in 96 patients with aSAH, Sanelli et al. performed ROI-based CTP between Days 6 and 8 after aSAH and found a sensitivity of 78% and a specificity of 66% of CTP for the development of permanent neurological deficits and a sensitivity of 88% and a specificity of 59% for the development of DCI.

Earlier Studies

Wintermark et al. performed a retrospective analysis of 27 patients with aSAH who were suspected to develop angiographic vasospasm and therefore underwent CTP/CTA, TCD, and DSA between Days 6 and 8 after the initial bleeding. They found a significant correlation of CTP/CTA findings with those of DSA. The most accurate CTP parameter (based on ROI analysis) in this study for the detection of angiographic vasospasm was MTT, with a cutoff at 6.4 seconds and a very high NPV of 98.7%. Sanelli et al. performed a retrospective analysis of a single ROI-based CTP in 75 patients between Day 0 and Day 3 after aSAH and found a statistically significant reduction of CBF and prolongation of MTT on early CTP in patients who develop angiographic vasospasm later. In a second retrospective study in 96 patients with aSAH, Sanelli et al. performed ROI-based CTP between Days 6 and 8 after aSAH and found a sensitivity of 78% and a specificity of 66% of CTP for the development of permanent neurological deficits and a sensitivity of 88% and a specificity of 59% for the development of DCI.

In a retrospective ROI-based CTP study by Kunze et al., 53 patients with aSAH were examined on Day 3 or 4, Day 6 or 7, Days 9 and 10, and additionally at any other

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ACoA = anterior communicating artery; BA = basilar artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCoA = posterior communicating artery; PICa = posterior inferior cerebellar artery; VA = vertebral artery.

* Values are expressed as the number (%).
time point when cerebral vasospasm was suspected. The CTP parameter with the highest sensitivity (93%) but a low specificity (27%) for the detection of angiographic vasospasm was TTP. With at least 3 CTP investigations per patient, the exposure to radiation was higher than in most other studies and in the present study. Killeen et al. performed ROI-based CTP in 97 consecutive aSAH patients between Days 6 and 8 and correlated in a retrospective analysis the CTP data with cerebral infarction and/or permanent neurological deficit. The sensitivity and specificity for the detection of infarction and/or permanent neurological deficit were 84% and 73%, respectively. Etminan et al. have shown that patients who later develop angiographic vasospasm have a higher incidence of fixed neurological deficits and DCI, but also parameters that are not closely linked to brain perfusion, such as age, hydrocephalus, and modality of aneurysm therapy. Thus, outcome might not be the ideal validating parameter.

A second limitation is time point and repetition of CTP investigation. In the current literature, an accepted time point for CTP does not exist. In some series, CTP was performed only in cases of clinical deterioration; in other series, up to 3 routine CTP scans were obtained. However, CTP at the moment of neurological decline might be too late for initiation of a successful antivasospastic therapy, whereas 3 routine CTPs might unnecessarily expose patients to radiation.

The ROIs represent a third limitation. Prediction of vascular territories in which hypoperfusion might occur is difficult. Therefore, preselection of ROIs carries the risk that areas of brain hypoperfusion remain undetected. Another limitation is study design; the vast majority of the published studies were retrospective analyses.

Rationale for the Present Study

The rationale for study initiation was to attempt to overcome some of the aforementioned limitations of other studies. We used an imaging algorithm to 1) identify patients and tissue at risk before occurrence of fixed neurological deficits and DCI, 2) reduce the number of repeated scans to a minimum, and 3) obtain CTP data from defined and therefore comparable time points after aSAH. We planned to perform the first CTP on Day 3 for 2 reasons. First, TCD studies indicated Days 4–14 to be the vasospasm period. Second, studies by Sanelli et al. and Etminan et al. have shown that patients who later develop angiographic vasospasm already had a CBF reduction and an MTT prolongation on a Day 0 to Day 3 CTP. In surgical cases, spatula pressure could induce prolonged frontal and temporal hypoperfusion; therefore, we refrained from CTP on Days 0–2. We were able to perform CTP on Day 3 in the vast majority of included patients, but CTP had to be postponed in 1 patient to Day 4 and in 3 patients to Day 5 due to a nonfunctioning CT scanner, which might represent a certain limitation of the study. However, according to the clinical and TCD criteria, none of these patients had vasospasm. CTP was repeated if 1) TCD suggested development of clinically relevant vasospasm using the criterion of a BFV increase > 50 cm/sec within 24 hours, or 2) intubation and sedation did not allow clinical monitoring. This algorithm was evaluated in a prospective study using whole-brain instead of ROI-based CTP.
Can CTP on Day 3 Predict DIND and DCI?

In the present study, 31% of all patients developed DIND, which is in line with the percentage previously described in the literature. 27,33 The most important result of the study was that whole-brain CTP routinely performed on Day 3 has a high sensitivity and specificity for the identification of patients at risk for the development of DIND, allowing early initiation or intensification of antivasospastic therapy. The sensitivity was 77%, which is comparable with the reported sensitivity of CTP in the vasospasm phase and only slightly lower compared with the sensitivity of CTP performed at the time of clinical deterioration, which could be too late to avoid permanent neurological deficits or infarction. The specificity of early whole-brain CTP was 87%, which was even higher than in other studies. Our results clearly indicate that whole-brain CTP scanning on Day 3 after aSAH has sufficient diagnostic accuracy with the lowest possible radiation exposure; it provides an early diagnosis, allowing for initiation of appropriate treatment.

Can TCD, as a Pretest, Reduce the Number of Additional CTP Investigations?

Transcranial Doppler sonography is an established monitoring tool for the identification of cerebral vasospasm after aSAH. With the aim to reduce the number of repeated CTP scans, we tried to use TCD for identification of patients at risk. Repeat CTP was only performed in patients with a BFV increase > 50 cm/sec within 24 hours. This was based on the study by Rätsep et al., who found a correlation of cerebral hemodynamic impairment with severe vasospasm and with a rapid increase in TCD-BFV. 30 We showed that an increase in TCD-BFV usually lags 1 or 2 days behind the identification of perfusion deficits shown by CTP. Accordingly, we found no statistically significant correlation between TCD-BFV increase and perfusion deficits on CTP. Thus, we can conclude that the parameter of TCD-BFV increase alone is not suitable for the detection of tissue at risk.

Concerning the detection of tissue at risk, whole-brain CTP should be an essential part of the diagnostic workup in addition to daily clinical assessment and daily BFV measurement by TCD. These findings are supported by the study by Pham et al., which evaluated the diagnostic accuracy of CTP and TCD for the prediction of DCI between Days 3 and 14 after aSAH. They performed qualitative visual analysis of the CTP maps and quantitative analysis based on predefined ROIs and found a good prediction of DCI by CTP at a median of 3 days before infarction manifestation. In line with our findings, TCD measurements failed to predict the occurrence of DCI. 24 In contrast, in a retrospective study of 45 patients with aSAH, Toi et al. reported that TCD in the early stage of aSAH can predict the future occurrence of symptomatic vasospasm. In their study, the highest sensitivity (71.4%) and specificity (68.1%) were seen on Day 3, with a BFV threshold of 72.5 cm/sec. 31

Whole-Brain CTP on Day 7 After aSAH in Patients Who Were Comatose and/or Sedated

The identification of impending DIND or DCI in patients with high-grade aSAH is difficult due to a decreased possibility of neurological assessment. Therefore, we repeated CTP on Day 7 after aSAH in patients who were comatose and/or sedated. Perfusion deficits were seen in 4 of the 7 patients who were comatose and/or sedated. Interestingly, the initial CTP had already demonstrated perfusion deficits in these patients, of whom all developed DCI. This suggests that the information gain by repeated CTP on Day 7 in patients who are comatose and/or sedated is low and too late for initiation of appropriate antivasospastic therapy. However, the number of patients is far too low to draw any final conclusion concerning the diagnostic value of CTP on Day 7 after aSAH in patients who are comatose and/or sedated.

Does CTP Improve Outcome?

The overall aim of using TCD and DSA for vasospasm identification, and of using CTP for identification of tissue at risk for DCI, was to improve outcome. We showed that early CTP has a high PPV and NPV for DIND and DCI. However, the study design did not allow us to determine if that high PPV translates into better outcome. All patients with proven territorial hypoperfusion in CTP and artery narrowing in CTA underwent further endovascular therapy and/or induced hypertension. However, the treatment was not standardized for purposes of the study, and treatment failure, which is frequent in patients with severe vasospasm despite timely recognition of tissue at risk by CTP, was not defined. We strongly believe that a larger study, which perhaps could not be conducted at a single center, would be necessary to address the issue of outcome improvement by CTP.

The study also did not allow us to answer the question of whether CTP is superior to routine angiography during the vasospasm period or to measurement of pito2 (brain tissue oxygen partial pressure), because no comparison between the tools was performed. However, the study allowed us to gain information on the value of CTP compared with clinical examination and TCD. We showed that 1) CTP on Day 3 (i.e., before the majority of patients become clinically symptomatic) has a high sensitivity and specificity for the identification of patients at risk for the development of DIND, and 2) the increase in TCD-BFV usually lags 1 or 2 days behind the identification of perfusion deficits by CTP. These findings suggest that early CTP might be a better tool than clinical examination and TCD for timely identification of patients at risk.

Strengths and Limitations of the Study

Strengths of this study include its prospective nature, the use of a rigid CTP algorithm, the focus on an increase in sensitivity as well as an avoidance of unnecessary radiation exposure, and the use of whole-brain CTP in patients with aSAH for the first time. We had to delay early CTP in 9% of patients to Days 4 and 5 due to logistic reasons, which might represent a limitation. However, none of the patients had clinical signs of vasospasm or BFV > 120 cm/sec. The number of included patients is still too small to consistently answer distinct questions in subgroup analyses. Furthermore, the results of the present study, as well as those of previous studies concerning sensitivity and speci-
ficacy, are hampered by the fact that the CTP findings led to initiation of therapies with varying efficacy to reverse the detected perfusion deficits.

Conclusions

Whole-brain CTP is a rapid imaging technique that allows early identification of patients at risk for developing DIND and tissue at risk for vasospasm-induced infarction within days after aSAH. On the basis of this study’s findings, a routine use of whole-brain CTP in the acute phase of aSAH seems to be useful.

References


Disclosures
Prof. Moerer gave lectures on mechanical ventilation and hemodynamic monitoring at regional workshops and industriesponsored sessions within the context of a national congress and received speaker’s honoraria from Pulsion Medical, Hill-Rom, and MAQUET Critical Care.

Author Contributions
Conception and design: Malinova, Moerer, Rohde, Mielke. Acquisition of data: Malinova, Dolatowski, Schramm. Analysis and interpretation of data: Malinova, Dolatowski, Schramm, Rohde, Mielke. Drafting the article: Malinova. Critically revising the article: Schramm, Moerer, Rohde. Reviewed submitted version of manuscript: Moerer, Rohde. Approved the final version of the manuscript on behalf of all authors: Malinova. Statistical analysis: Malinova. Administrative/technical/material support: Dolatowski, Schramm. Study supervision: Moerer, Rohde, Mielke.

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