Diagnostic Threshold Values of Cerebral Perfusion Measured With Computed Tomography for Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—Early diagnosis of delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage is critical but difficult. We analyzed diagnostic threshold values of CT perfusion for use in detection of DCI in patients with subarachnoid hemorrhage.

Methods—We prospectively enrolled patients with subarachnoid hemorrhage with CT perfusion on admission and at time of clinical deterioration or after 1 week if no deterioration occurred. The gold standard was the clinical diagnosis of DCI based on all clinical, laboratory, and imaging data except CT perfusion. Patients with failed imaging (n=6) and other causes of deterioration (n=45) were excluded for the current study. We measured CT perfusion values, including cerebral blood volume, blood flow, mean transit time (MTT), and time to peak in predefined regions of interest and then compared absolute perfusion and perfusion asymmetry for patients with and without DCI. Diagnostic threshold values for DCI were evaluated and sensitivity and specificity calculated for optimal thresholds.

Results—Of 85 eligible patients with subarachnoid hemorrhage, 50 had DCI; 35 patients with no clinical deterioration comprised the reference group. Cerebral blood flow was significantly lower, MTT higher, and perfusion asymmetry larger in patients with DCI. We found that largest absolute MTT and the MTT difference between hemispheres were good diagnostic tests. Diagnostic threshold values with optimal sensitivity and specificity were an MTT of 5.9 seconds and an MTT difference of 1.1 second.

Conclusion—Thresholds for absolute MTT values and between-hemisphere MTT differences on CT perfusion can distinguish between patients with delayed cerebral ischemia and clinically stable patients. (Stroke. 2010;41:00-00.)

Key Words: cerebral hemodynamics ■ CT ■ ischemia ■ subarachnoid hemorrhage

Delayed cerebral ischemia (DCI) is a severe and frequent complication of aneurysmal subarachnoid hemorrhage (SAH). It typically occurs in the first 2 weeks after the initial hemorrhage and increases the risk of poor outcome in patients who survive the first days.1 The onset of DCI is characterized by a gradual decrease in consciousness, new focal deficit, or both. The clinical course of the symptoms and CT evaluation ≥1 days after onset of symptoms are often helpful in ruling DCI in or out. Establishing the diagnosis ≥1 days after onset is however not meaningful if treatment decisions need to be made. For these decisions, diagnosing DCI early in its course is pivotal but notoriously difficult, because the onset of DCI is often insidious and there is a long list of other causes of deterioration. Increasing edema around a parenchymal hematoma, rebleeding from the aneurysm, (increasing) hydrocephalus, cardiac insufficiency, pulmonary edema, infection, and metabolic disturbances may also cause a decrease in consciousness or focal deficit and thus mimic DCI. When clinical deterioration occurs, a noncontrast CT scan (NCT) is routinely performed to rule out intracerebral causes other than DCI. However, NCT is not very sensitive in detecting early ischemia.2 The presence of cerebral vasospasm identified with transcranial Doppler, digital subtraction angiography, or CT angiography (CTA) is frequently used to confirm DCI. Presence of vasospasm, however, does not prove the presence of ischemia,3 and absence of vasospasm does not rule out ischemia.4,5 Better diagnostic tests in the acute stage of deterioration, possibly caused by DCI, are therefore needed.

In patients with ischemic stroke, CT perfusion (CTP) is an established tool to detect early ischemia.2,6-7 In patients with SAH, CTP has recently been shown to be promising for this purpose.2 Absolute threshold values would simplify the detection of DCI, but these values are not yet available.
The purpose of this study was to assess absolute and relative (interhemispheric ratios and differences) threshold values of CTP parameters for the diagnosis of DCI in patients with SAH.

Materials and Methods

Design
In our hospital, all patients with SAH routinely undergo NCT, CTP, and CTA on admission to evaluate the presence and configuration of aneurysms and at the time of deterioration to identify the cause of deterioration. We prospectively enrolled all patients with SAH admitted to our hospital between May 2007 and September 2009 who met the following inclusion criteria: (1) ≥18 years of age; (2) aneurysmal cause of SAH; (3) admitted within 72 hours after SAH; and (4) written informed consent.

Patients without clinical deterioration underwent NCT and CTP approximately 1 week after admission. No CTA was performed in these clinically stable patients to limit the radiation dose. Patients with impaired renal function (creatinine >200 μmol/L) or other contraindications for contrast-enhanced CT scans, including pregnancy, were excluded.

Included patients with a clinical deterioration during their clinical course from other causes than DCI were excluded from further analyses. Patients without clinical deterioration served as a reference group (non-DCI).

For all included patients, we recorded age, gender, clinical status on admission (according to the World Federation of Neurological Surgeons scale), amount of blood on the admission scan (Hijdra score), aneurysm location and treatment, and in patients with clinical deterioration, presence of angiographic vasospasm on CTA. The study was approved by our hospital’s ethics committee. All patients were treated according to the SAH treatment protocol of our hospital, consisting of absolute bed rest until aneurysm treatment, oral nimodipine, cessation of antihypertensive medication, intravenous fluids, and CTA on admission to evaluate the presence and configuration of aneurysms and at the time of deterioration to identify the cause of deterioration.

Delayed Cerebral Ischemia
For the purpose of the study, the diagnosis of DCI in patients who experienced clinical deterioration (decreased Glasgow Coma Scale of at least 2 points lasting >2 hours or a new focal deficit) was assessed after completion of the clinical course. This was based on prospectively collected data by 2 neurologists (N.K.d.R. and C.J.M.F.) as described previously. The 2 neurologists had full access to all clinical information concerning the patient’s entire clinical course both before and after clinical deterioration, all laboratory results, and all NCTs but were blinded for the CTP. The NCTs were used to show ischemic changes and exclude rebleeding, hydrocephalus, edema around a hematoma, and postoperative swelling. The clinical information and laboratory results were used to exclude infection or metabolic disturbances as a cause of the deterioration.

Imaging Protocol
CTP imaging is an accurate technique to calculate information on cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak (TTP). CTA can be used to accurately detect vasospasm.

Imaging studies were executed on a 16-slice or 64-slice spiral CT scanner (PhilipsMX8000 LDT, Best, The Netherlands) using previously published scanning protocols. The CTP scan covered a 2.4- to 4-cm slab selected at the level of the basal ganglia.

Image Postprocessing and Evaluation
CTP scans were reconstructed at 6-mm (16-slice) and 5-mm (64 slice) contiguous axial images. Absolute perfusion maps of CBV, CBF, MTT, and TTP were calculated using commercially available Philips software (Extended Brilliance Workspace 3.4.x). On all follow-up scans, perfusion was measured in regions of interest (ROIs) that were drawn by hand bilaterally in the cortical gray matter and basal ganglia of the flow territories of the anterior and middle cerebral artery.

Figure 1. ROIs drawn by hand bilaterally in the cortical gray matter and basal ganglia of the flow territories of the anterior and middle cerebral artery.

Analysis
In all analyses, we compared patients with DCI with clinically stable patients (non-DCI). For the analysis of absolute CTP threshold values, we selected the ROI with the lowest absolute values of CBV and CBF and highest absolute values of MTT and TTP (reflecting the least perfused flow territories) in each patient. Because absolute perfusion values can be influenced by observer-dependent postprocessing steps, we also used relative measurements. For each ROI, we calculated interhemispheric ratios (lowest to highest) for CBV and CBF, and interhemispheric differences (highest minus lowest) for MTT and TTP for all ROIs. For each patient, the lowest (closest to zero) CBV and CBF ratio and the largest MTT and TTP difference (reflecting the largest asymmetry in perfusion between both hemispheres) were selected. Because both absolute and relative values were not normally distributed, the median and the interquartile range...
for each parameter were calculated. The values of DCI and non-DCI patients were compared using the Mann–Whitney U test.

To obtain diagnostic threshold values of perfusion, we used receiver operator characteristic (ROC) curves. These curves were made for absolute values of the least perfused ROI and for the relative values of the ROI with the largest perfusion asymmetry (ratio closest to zero or largest difference). An area under the curve of \(AUC/0.75\) is considered to be a good test.13 From the ROC curve, we derived optimal threshold values to distinguish between patients with and without DCI by seeking the best tradeoff between highest possible sensitivities and specificities of the threshold values. For the sensitivity and specificity of the optimal threshold value, a 95% Wilson score interval was calculated. Sensitivity and specificity were used to create likelihood ratio graphs, which make it possible to visually compare all diagnostic properties of a test.14

### Results

One hundred thirty-six patients were enrolled in the study, of which 6 were excluded because the follow-up images could not be evaluated due to motion artifacts. Of the remaining 130 patients, 50 had DCI; 35 patients remained clinically stable and served as our reference group (non-DCI); and 45 patients were excluded from further analyses because the cause of clinical deterioration was not DCI but progression of edema around an existing intracerebral hematoma (8), the neurosurgical/coiling procedure (15), rebleeding (3), hydrocephalus (9), severe infectious/metabolic disturbance (8), epilepsy (1), and increasing subdural hygroma (1).

The patient characteristics of the 50 patients with DCI and the 35 non-DCI patients are shown in Table 1. Of all patients with DCI, 66% had moderate or severe vasospasm in vessel segments on CTA.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DCI</th>
<th>No DCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>No. of men</td>
<td>12 (24%)</td>
<td>12 (34%)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>55 (26–81)</td>
<td>57 (18–79)</td>
</tr>
</tbody>
</table>

### Table 2. Median Values and P Value (Mann–Whitney U Test) Between Patients With and Without DCI of Absolute (ROIs With Lowest CBF and CBV and Highest MTT and TTP) and Relative (Lowest CBF and CBV Ratios and Largest MTT and TTP Differences Between Hemispheres) Differences

<table>
<thead>
<tr>
<th></th>
<th>DCI (Interquartile Range 25–75%)</th>
<th>No DCI (Interquartile Range 25–75%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBV, mL/100 g</td>
<td>2.77 (2.32–3.32)</td>
<td>2.85 (2.52–3.31)</td>
<td>0.262</td>
</tr>
<tr>
<td>CBF, mL/100 g/min</td>
<td>30.6 (20.7–37.6)</td>
<td>38.4 (31.2–45.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>MTT, seconds</td>
<td>6.65 (5.62–8.75)</td>
<td>5.34 (4.51–5.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TTP, seconds</td>
<td>26.5 (22.6–29.7)</td>
<td>24.3 (23.1–26.6)</td>
<td>0.119</td>
</tr>
<tr>
<td>CBV ratio</td>
<td>0.74 (0.63–0.84)</td>
<td>0.82 (0.71–0.87)</td>
<td>0.031</td>
</tr>
<tr>
<td>CBF ratio</td>
<td>0.67 (0.45–0.77)</td>
<td>0.78 (0.69–0.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>MTT difference, seconds</td>
<td>1.91 (1.10–3.89)</td>
<td>0.96 (0.67–1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TTP difference, seconds</td>
<td>1.34 (0.80–2.89)</td>
<td>0.70 (0.47–1.22)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*In clinically stable patients, no CTA was performed to minimize the additional radiation dose.

WFNS indicates World Federation of Neurological Surgeons.

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largest interhemispheric MTT and TTP differences are shown in Figure 2B. The optimal threshold values for diagnosing DCI extracted from the ROC curves (Figure 2A–2B) were used to create likelihood ratio graphs (Figure 2C–D). The areas under the ROC curves and the optimal threshold values with their sensitivity and specificity are shown in Table 3. Largest absolute MTT and largest MTT and TTP difference had areas under the curve >0.75 and can therefore be considered to be a good diagnostic test. The threshold for absolute MTT and MTT differences had the best diagnostic properties (Figure 2D).

Figure 3 shows an example of how the MTT difference threshold can be applied to make perfusion abnormalities more easily visible in a patient with SAH with reversible and irreversible areas of DCI.

**Table 3. Sensitivity and Specificity With 95% CIs of Optimal CTP Threshold Values for Diagnosing DCI**

<table>
<thead>
<tr>
<th></th>
<th>AUC (95% CI)</th>
<th>Threshold</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBV, mL/100 g</td>
<td>0.57 (0.45–0.70)</td>
<td>2.78</td>
<td>0.52 (0.45–0.58)</td>
<td>0.63 (0.54–0.69)</td>
</tr>
<tr>
<td>CBF, mL/100 g/min</td>
<td>0.71 (0.60–0.82)</td>
<td>36.3</td>
<td>0.74 (0.66–0.78)</td>
<td>0.63 (0.54–0.69)</td>
</tr>
<tr>
<td>MTT, seconds</td>
<td>0.76 (0.66–0.86)</td>
<td>5.85</td>
<td>0.70 (0.62–0.74)</td>
<td>0.77 (0.67–0.81)</td>
</tr>
<tr>
<td>TTP, seconds</td>
<td>0.60 (0.48–0.72)</td>
<td>25.2</td>
<td>0.54 (0.47–0.60)</td>
<td>0.63 (0.54–0.69)</td>
</tr>
<tr>
<td>CBV ratio</td>
<td>0.64 (0.52–0.76)</td>
<td>0.80</td>
<td>0.64 (0.57–0.69)</td>
<td>0.63 (0.54–0.69)</td>
</tr>
<tr>
<td>CBF ratio</td>
<td>0.72 (0.61–0.83)</td>
<td>0.77</td>
<td>0.76 (0.68–0.80)</td>
<td>0.63 (0.54–0.69)</td>
</tr>
<tr>
<td>MTT difference</td>
<td>0.78 (0.68–0.87)</td>
<td>1.08</td>
<td>0.80 (0.72–0.83)</td>
<td>0.63 (0.54–0.69)</td>
</tr>
<tr>
<td>TTP difference</td>
<td>0.75 (0.65–0.86)</td>
<td>0.99</td>
<td>0.70 (0.62–0.74)</td>
<td>0.66 (0.57–0.72)</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve.

**Discussion**

We assessed absolute and relative (interhemispheric ratios and differences) CTP threshold values to discriminate between patients with DCI and clinically stable patients (non-DCI). Patients with DCI had significantly larger perfusion asymmetry, lower CBF, and longer MTT than non-DCI patients. MTT showed the best diagnostic values for DCI with highest areas under the ROC curve for both absolute and relative MTT measurements.

In agreement with previous studies,3,15 our results show that there are differences in cerebral perfusion and perfusion asymmetry between patients with DCI and clinically stable patients. Differences between the 2 groups are however not adequate enough for diagnostic purposes in the individual
patient. The threshold values presented in this article can distinguish patients with DCI from clinically stable patients and are an important step toward individual diagnostics necessary to guide treatment. Thresholds for absolute and relative MTT had the best diagnostic properties, whereas CBV had the worst properties. Apparently, MTT abnormalities occur in patients with DCI with CBV remaining relatively stable and almost equal to the CBV in non-DCI patients. This is comparable to the penumbral tissue in acute ischemic stroke indicating that the ischemia may still be reversible in the measured area.6-7 The fact that CBV is not increased in the presence of a prolonged MTT is compatible with disturbed cerebral autoregulation in patients with DCI.16 Overall, relative threshold values had better diagnostic properties than absolute measurements. The reason for this may be that relative measurements reduce the variability caused by (observer-dependent) postprocessing steps.12

Determining threshold values with good diagnostic properties for DCI in patients with SAH is quite challenging. First, perfusion measurements may be blurred by other pathological conditions inherent to SAH and SAH treatment.17,18 Although these conditions were not the cause of deterioration in our DCI group, the presence of hydrocephalus, parenchymal hemorrhage, temporary vessel occlusion during surgical or angiographic interventions, and edema may have affected cerebral perfusion in addition to DCI. Second, the duration and extent of DCI most likely influence our results. DCI can be transient and multifocal.19,20 For example, in some patients, the neurological condition was already improving at the time of scanning and thus perfusion deficits may have diminished. Also, some of our patients had visually apparent bilateral ischemia on CTP resulting in less asymmetry than in patients with unilateral ischemia. In these patients, the absolute threshold values may be more useful, indicating that both threshold values should always be applied for optimal results.

Third, we performed measurements of perfusion in predefined ROIs. This is necessary to objectively test the diagnostic ability of CTP and minimize observer bias. However, differences may be less conspicuous due to perfusion measurements not being centered to the ischemic area. Selecting the ROI in visible areas of hypoperfusion would probably result in better diagnostic performance. Studies reporting on absolute perfusion measured in visually selected ROIs showed lower CBF and higher MTT values than reported in our study.3,15 A recent study using only visual assessment of CTP color maps without absolute or relative measurements found a positive and negative predictive value of 0.88 and 0.73 for DCI in a population of patients with SAH with clinical deterioration.2 However, interpreting CTP color maps in patients with SAH requires experienced readers, which reduces generalizability and use during out-of-office hours. The presented diagnostic thresholds may simplify the diagnosis (Figure 3). The color-coded map in Figure 3, indicating DCI based on thresholds for relative MTT measurements, could be used in future research to see if other pathology causing decreased perfusion can be distinguished from DCI by visual interpretation. In this way, objective measurements and knowledge on clinical condition and features can be combined. Furthermore, future research is needed to assess whether DCI can be identified before symptoms occur, to predict whether ischemia at the time of deterioration is reversible or will lead to permanent infarction, and to study the influence of therapeutic interventions on tissue fate.

There are some issues to our study that need further explanation. Because all patients with other causes for deterioration than DCI were excluded, we could not calculate predictive values from our threshold values. Moreover, the absolute and relative values of perfusion overlap considerably between DCI and non-DCI patients in our population. For any chosen threshold value, there will thus be a considerable number of false-positive and false-negative measurements. These problems regarding the practical application of perfusion values have also been described in ischemic stroke in which identification of the ischemic penumbra (salvageable brain tissue) is the main goal. Reported optimal threshold values for the penumbra vary widely and are not yet generally applicable.21 Clearly, our threshold values will also need to be validated and tested for reproducibility in another series of patients including all patients with serious comorbidity.

Another issue is that our gold standard for DCI did not require the presence of hypodensities on follow-up imaging. We thereby identified all patients with symptomatic ischemia and not just patients with ischemia that turns into permanent infarction. The absence of hypodensities does not rule out the
intensive care patients, is time-consuming, more expensive, and might be considered a weakness of our study. However, in our opinion, presence of vasospasm is not relevant in the absence of clinical symptoms.2

The use of CTP for the evaluation of DCI results in an additional exposure to radiation ranging between 1.1 and 5.0 mSv depending on the used parameters.22 An effective dose of 5 mSv results in an additional risk of cancer of 0.025% compared with unexposed individuals.22 However, because diagnosing DCI with CTP facilitates adequate treatment of DCI, resulting in reduced mortality and morbidity,1 this additional risk may be justified.23 Perfusion imaging with MRI is possible without radiation24 but less suited for intensive care patients, is time-consuming, more expensive, and less available outside regular working hours.

Summary
Patients with DCI have larger perfusion asymmetry and decreased absolute perfusion than patients with no deterioration after SAH. Threshold values of absolute and relative perfusion measurements in patients with SAH can be used to diagnose DCI. Absolute MTT values and interhemispheric MTT differences have good diagnostic properties to distinguish patients with DCI from clinically stable patients.

The presented threshold values are an important step toward individualized diagnostics of DCI in patients with SAH but require further validation.

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Disclosures
None.

References
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