Diagnosing Delayed Cerebral Ischemia With Different CT Modalities in Patients With Subarachnoid Hemorrhage With Clinical Deterioration

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Background and Purpose—Delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage worsens the prognosis and is difficult to diagnose. We investigated the diagnostic value of noncontrast CT (NCT), CT perfusion (CTP), and CT angiography (CTA) for DCI after clinical deterioration in patients with subarachnoid hemorrhage.

Methods—We prospectively enrolled 42 patients with subarachnoid hemorrhage with clinical deterioration suspect for DCI (new focal deficit or Glasgow Coma Scale decrease ≥2 points) within 21 days after hemorrhage. All patients underwent NCT, CTP, and CTA scans on admission and directly after clinical deterioration. The gold standard was the clinical diagnosis DCI made retrospectively by 2 neurologists who interpreted all clinical data, except CTP and CTA, to rule out other causes for the deterioration. Radiologists interpreted NCT and CTP images for signs of ischemia (NCT) or hypoperfusion (CTP) not localized in the neurosurgical trajectory or around intracerebral hematomas, and CTA images for presence of vasospasm. Diagnostic values for DCI of NCT, CTP, and CTA were assessed by calculating sensitivities, specificities, positive predictive values, and negative predictive values with 95% CIs.

Results—In 3 patients with clinical deterioration, imaging failed due to motion artifacts. Of the remaining 39 patients, 25 had DCI and 14 did not. NCT had a sensitivity of 0.56 (95% CI, 0.37 to 0.73), specificity = 0.71 (0.57 to 0.77), positive predictive value = 0.78 (0.55 to 0.91), negative predictive value = 0.48 (0.28 to 0.68); CTP: sensitivity = 0.84 (0.65 to 0.94), specificity = 0.79 (0.52 to 0.92), positive predictive value = 0.88 (0.69 to 0.96), negative predictive value = 0.73 (0.48 to 0.89); CTA: sensitivity = 0.64 (0.45 to 0.80), specificity = 0.50 (0.27 to 0.73), positive predictive value = 0.70 (0.49 to 0.84), negative predictive value = 0.44 (0.23 to 0.67).

Conclusion—As a diagnostic tool for DCI, qualitative assessment of CTP is overall superior to NCT and CTA and could be useful for fast decision-making and guiding treatment. (Stroke. 2009;40:3493-3498.)

Key Words: computed tomography ■ ischemia ■ perfusion ■ subarachnoid hemorrhage ■ vasospasm

Delayed cerebral ischemia (DCI) is a serious complication of aneurysmal subarachnoid hemorrhage (SAH). It typically occurs 4 to 12 days after initial bleeding and increases the risk of poor outcome in patients who survive the first days.1 The onset of DCI is characterized by a decrease in consciousness, new focal deficit, or both. There is, however, no good diagnostic test to confirm the presence or absence of DCI at the time of clinical deterioration.

When clinical deterioration occurs, a noncontrast CT scan (NCT) is usually made to rule out rebleeding, swelling around an intracerebral hematoma, and hydrocephalus. NCT is, however, not very sensitive in showing early ischemia.2 If NCT renders no explanation, and no clear signs of severe infection or metabolic disturbance are present, it is often assumed that the patient has DCI. This diagnosis is sometimes confirmed on later follow-up imaging showing one or more areas of cerebral infarction. However, when infarction is seen on these follow-up images, it is too late to treat the patient. Therefore, ischemia should be identified before it turns into infarction. To diagnose DCI when symptoms occur, presence of vasospasm shown with transcranial Doppler or angiography is frequently used. Although traditionally vasospasm is thought to be the main cause for DCI, vasospasm can be present without DCI and DCI can be present without vasospasm.3–5 Better diagnostic tools are thus needed to identify DCI at the time of deterioration, which is important to facilitate rapid treatment decision-making.

In patients with occlusive stroke, early ischemic changes can be accurately identified in the acute stage with CT perfusion (CTP).6,7 Because infarction in DCI is preceded by a decreased cerebral perfusion,8,9 CTP may be a useful tool to identify ischemia as the cause of clinical deterioration.

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The purpose of this study was to evaluate the diagnostic value of NCT, CTP, and CT angiography (CTA) for DCI in patients with SAH with clinical deterioration.

## Materials and Methods

### Design
We prospectively enrolled all patients with SAH admitted to the University Medical Center Utrecht from May 2007 until June 2008 who underwent the SAH imaging protocol of our institution (NCT, CTP, and CTA) on admission and met the following inclusion criteria: (1) ≥18 years of age; (2) aneurysmal cause of SAH; (3) admitted within 72 hours after SAH; and (4) clinical deterioration (decreased Glasgow Coma Scale of at least 2 points lasting >2 hours or new focal deficit) within 21 days after hemorrhage.

Patients were treated according to the SAH treatment protocol of our hospital, which includes oral nimodipine, fluid management to prevent hypovolemia, and evaluation for clinical deterioration (every 2 to 4 hours). When deterioration occurred, patients were again scanned with our SAH imaging protocol. Patients with impaired renal function (creatinine >200 μmol/L) or other contraindications for contrast-enhanced CT scans as well as pregnant women were excluded. For all included patients, 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 time of clinical deterioration were recorded. The study was approved by our ethics committee.

### Delayed Cerebral Ischemia
The occurrence of DCI was retrospectively assessed by 2 neurologists (N.K.d.R. and C.J.M.F.) who had full access to all clinical information concerning the entire period of the patient's entire clinical course, both before and after clinical deterioration, all laboratory results, and the NCT performed at the time of the clinical deterioration but who were blinded to the CTP and CTA images. The NCT was used to exclude rebleeding, hydrocephalus, edema around a hematoma and postoperative swelling. The clinical information and laboratory findings were used to exclude infection or metabolic disturbances as a cause for the deterioration. Infection was defined as fever, leucocytosis, increased C-reactive protein, or positive cultures along with clinical signs of infection for which antibiotic treatment was indicated. Metabolic disturbances were defined as hypo- or hypernatremia (<125 mmol/L or >155 mmol/L), hypoponemagsemia (<0.6 mmol/L), or hypercalcemia (ionized calcium >1.3 mmol/L). This clinical diagnosis served as the gold standard.

### Imaging Protocol
All patients underwent NCT, CTP, and CTA imaging on admission and at the time of clinical deterioration. CTP imaging measures cerebral perfusion on the tissue level and provides accurate data compared to the gold standard xenon CT.\(^\text{11}\) CTP gives information on cerebral blood volume, cerebral blood flow, and mean transit time. CTA can be used for detection of vasospasm with accuracy equal to that of the gold standard digital subtraction angiography.\(^\text{12}\)

All imaging studies were executed on a 64-slice spiral CT scanner (Philips Mx8000 LDT, Best, The Netherlands). The CTP scan covered a 4-cm slab selected at the level of the basal ganglia. For the CTA scan, 40 mL of nonionic contrast agent (ipromide, Ultravist, 300 mg iodine/mL; Schering, Berlin, Germany) was injected into the cubital vein at a rate of 5 mL/s followed by a 40-mL saline flush at a rate of 5 mL/s using a Stellant Dual CT injector (Medrad Europe BV, Beek, The Netherlands). The following parameters were used: 80 kVp, 150 mAs, 64×0.625-mm collimation, 512×512 matrix, 220-mm field of view, one image per 2 seconds during 60 seconds.

For the CTA scan, 70 mL of nonionic contrast agent was injected into the cubital vein: 50 mL at a rate of 5 mL/s followed by a 40 mL saline flush at a rate of 4 mL/s. Scanning was performed with: 80/120 kVp, 300/100 mAs, 64×0.625-mm collimation, 512×512 matrix, 200 field of view, slice thickness 0.67 mm, and reconstruction increment 0.33 mm.

### NCT, CTP, and CTA Postprocessing and Evaluation
NCT scans were evaluated on a PACS (Picture Archiving and Communication System) station by 2 independent radiologists (I.C.v.d.S. and B.K.V.) who had information on the patient’s state of consciousness and presence and location of focal deficits at time of the CT scan, which resembles the clinical situation, and who were blinded to the CTP and CTA results. Positive findings were ischemic changes not localized in the neurosurgical trajectory or around an intracerebral hematoma (ICH). Ischemic changes consisted of hypodensities and loss of gray white matter differentiation. Consensus was reached for all images.

CTP scans were reconstructed at 5-mm contiguous axial images. Data were transferred to a Philips workstation for postprocessing. The CTP algorithm was based on the central volume principle, which is the most accurate for low injection rates of iodinated contrast
deterioration could not be evaluated due to motion artifacts. The characteristics of the 39 remaining patients and time of clinical deterioration are shown in Table 1.

Twenty-five patients were diagnosed with DCI and 14 patients were diagnosed with other causes for clinical deterioration than DCI. These causes were: progression of edema around an existing intracerebral hematoma (5 patients), the neurosurgical procedure (2 patients), rebleeding (2 patients), hydrocephalus (2 patients), and infectious/metabolic disturbance (3 patients).

The imaging findings of all patients are summarized in Figure 1. From the numbers in Figure 1, sensitivities, specificities, negative predictive value, and positive predictive value were calculated (Table 2) and likelihood ratios graphs were constructed (Figure 2B). Figure 2B shows that CTP has overall superior diagnostic quality for DCI compared to NCT and CTA, and NCT has overall superior diagnostic quality over CTA. Taking into account moderate vasospasm as well as severe vasospasm reduces the diagnostic quality of CTA for DCI compared to only severe vasospasm. Figure 3 shows examples of the imaging findings in patients with SAH with clinical deterioration.

### Analysis

To evaluate the diagnostic value of NCT, CTP, and CTA for DCI, 2×2 tables were made to calculate the sensitivity, specificity, negative predictive value, and positive predictive value of the three modalities (with 95% CIs calculated as Wilson score intervals). From these values, likelihood ratios graphs were created. These graphs are comparable to standard receiver operating characteristic curves, which are designed to determine the optimal diagnostic cutoff point of continuous variables. Because the determinants we used were not continuous but binary, we used likelihood ratios graphs instead of receiver operating characteristic curves. In these graphs, the difference in diagnostic quality of different tests (NCT, CTP, CTA) can be easily read by the relative position of their likelihood ratios graphs. This method takes into account all aspects (sensitivity, specificity, likelihood ratio of a negative test, and likelihood ratio of a positive test) of differences in diagnostic quality, which is a great advantage over comparing areas under the receiver operating characteristic curve, in which only sensitivity and specificity are taken into account.

### Results

Forty-two patients met our inclusion criteria. Three patients were excluded because the images made at the time of clinical deterioration could not be evaluated due to motion artifacts. The characteristics of the 39 remaining patients and time of clinical deterioration are shown in Table 1.

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### Table 2. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) With 95% CIs (Wilson score interval) for Diagnosing DCI of Positive Findings on NCT, Positive Findings on CTP, Moderate to Severe Vasospasm on CTA, and Severe Vasospasm on CTA*

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>NCT</td>
<td>0.56 (0.37–0.73)</td>
<td>0.71 (0.45–0.88)</td>
<td>0.78 (0.55–0.91)</td>
<td>0.48 (0.28–0.68)</td>
</tr>
<tr>
<td>CTP</td>
<td>0.84 (0.65–0.93)</td>
<td>0.79 (0.52–0.92)</td>
<td>0.88 (0.69–0.96)</td>
<td>0.73 (0.48–0.89)</td>
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<tr>
<td>CTA</td>
<td>0.64 (0.45–0.80)</td>
<td>0.50 (0.27–0.73)</td>
<td>0.70 (0.49–0.84)</td>
<td>0.44 (0.23–0.67)</td>
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<tr>
<td>Moderate to severe</td>
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<tr>
<td>vasospasm</td>
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<tr>
<td>CTA</td>
<td>0.40 (0.23–0.59)</td>
<td>0.71 (0.45–0.88)</td>
<td>0.71 (0.45–0.88)</td>
<td>0.40 (0.23–0.45)</td>
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<td>severe vasospasm</td>
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<td>0.40 (0.23–0.59)</td>
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*CTP is overall superior to NCT and CTA.
Discussion

In this study, we used a qualitative interpretation of NCT, CTP color maps, and CTA to diagnose DCI in patients with SAH with clinical deterioration. Our results show that the diagnostic value of areas of low perfusion on CTP is superior to ischemic findings on NCT and far superior to vasospasm on CTA in diagnosing DCI in patients with SAH with clinical deterioration.

A positive diagnosis of DCI is clinically very relevant to guide treatment. Hyperdynamic therapy (hypertension, hypervolemia, hemodilution, or triple H) is frequently used to treat DCI. However, it has not equivocally been proven that hyperdynamic therapy improves neurological outcome, and the use of this therapy has been associated with an increased risk of severe complications. Therefore, physicians are quite reluctant to apply hyperdynamic therapy if the diagnosis is not certain. Certainty in the diagnosis of DCI will increase with the large positive predictive value (0.88) of CTP and in a much lesser extent with NCT and CTA.

Our results emphasize the known limitations of the diagnostic value of NCT in detecting early ischemia. Of note is that the NCT at the time of deterioration was also part of our gold standard to define DCI, mainly to exclude rebleeding and hydrocephalus. The gold standard was furthermore based on clinical signs, blood analysis, and short-term clinical follow-up. However, we cannot rule out the possibility that ischemic lesions on the NCT were used to qualify the patient as having DCI. Therefore, incorporation bias may have caused an overestimation of the diagnostic value of NCT for DCI.

Our results also show that presence of vasospasm on CTA is not very helpful in diagnosing DCI. This confirms the findings of other investigators who showed that the positive predictive value of vasospasm for DCI is only 0.67. Although the degree of vasospasm is related to cerebral perfusion, presence of vasospasm does not mean that there is ischemia and absence of vasospasm does not mean that there is no ischemia. Vasospasm may therefore not be the sole cause of DCI and using angiographic vasospasm as a gold standard for DCI may cause many missed cases of DCI in patients with SAH with clinical deterioration.

Cerebral perfusion as seen on CTP reflects the net effect of all factors that contribute to the development of DCI. In stroke, CTP is already being used to show hypoperfused areas that are at risk for infarction. Hypoperfused areas in patients with SAH should in our opinion be interpreted in the same way. The false-positive and false-negative CTP findings in our results can be explained in the following ways. First, false-positive CTP findings can be a result of our definition of DCI in which we did not take into account that DCI could coexist with other pathology. For example, if no ischemic changes were seen on NCT and there clearly was other pathology that could cause clinical deterioration, like hydrocephalus, the deterioration was classified as other than DCI, although, in fact, DCI could have coexisted. This may have biased the results toward a lower diagnostic value of CTP. Second, false-negative findings can be a result of the limited brain coverage with 64-slice CTP when abnormalities are outside of the scanned area. Scanners with an increased detector range are currently coming on the market. False-negative CTP findings can also result from the fact that CTP color maps were interpreted without knowledge of clinical condition. A radiologist will generally find more abnormalities when knowing what to look for. In contrast to this, information about the patient’s state of consciousness and presence and location of focal deficits was available for the interpretation of NCT images.

Some limitations of our study should be considered. First, we did not use hypodensities on follow-up imaging as an obligatory criterion for DCI. Although hypodensities on follow-up may prove that ischemia has occurred, one cannot be sure at what time point this has occurred. Also, the absence of hypodensities does not rule out the possibility that DCI has
occurred; the hypoperfused areas on CTP or vasospasm on CTA may have been only transient, either because the patient received treatment or because it spontaneously resolved. We have seen patients with large perfusion deficits at the time of deterioration that resolved and left no hypodensities on follow-up imaging. These aspects make follow-up imaging less relevant when looking for a diagnostic tool to identify the cause of deterioration in patients with SAH.

Another limitation concerns the use of dynamic imaging techniques in the studied population. Patients with SAH are often restless, which can result in suboptimal images. Two patients were excluded for this reason.

One of our goals was to see if CTP could be helpful in diagnosing DCI at the time of clinical deterioration. Although the sample size of our study was relatively small, the current results show that CTP may indeed be a useful diagnostic tool in diagnosing DCI. However, before CTP can be implemented in clinical practice, generalizability, including interobserver variability, and feasibility should be assessed. Finally, although our qualitative approach seems to be sufficient in identifying perfusion defects, future research should focus on calculating quantitative threshold values from CTP data, which will also make it possible to assess the effects of DCI treatment.

Summary

We evaluated several CT imaging modalities to add more certainty to the uncertain diagnosis of DCI at the time of clinical deterioration. According to our results, CTP has superior diagnostic value compared to NCT and CTA. We therefore strongly suggest that future research on DCI should not focus on angiographic vasospasm, but rather on perfusion abnormalities in combination with clinical findings. CTP can render a fast diagnosis of DCI, which could help the physician in his or her decision-making and in guiding treatment.

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Disclosures

None.

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