Prognostic Value of Cerebral Perfusion–Computed Tomography in the Acute Stage After Subarachnoid Hemorrhage for the Development of Delayed Cerebral Ischemia

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Background and Purpose—Delayed cerebral ischemia (DCI) is an important cause of death and disability after subarachnoid hemorrhage. We studied the additional prognostic value of brain perfusion to 3 established predictors (age, clinical condition on admission, and amount of subarachnoid blood) for the development of DCI.

Methods—We included 69 patients scanned with perfusion–computed tomography within 72 hours after subarachnoid hemorrhage. For each patient, we determined cerebral blood flow (CBF) ratios of prespecified opposite regions of interest and the 3 established predictors. We calculated adjusted hazard ratios (HRs) for the CBF ratio and the 3 established predictors by means of multivariate analysis (Cox regression). The additional prognostic value of CBF ratios was assessed by comparing the area under the receiver operating characteristic curve (AUC) of 2 models: 1 with and 1 without addition of the CBF ratio to the 3 established predictors.

Results—The CBF ratio was an independent predictor for the development of DCI (HR, 0.63; 95% CI, 0.46 to 0.86) as was clinical condition (HR, 1.47; 95% CI, 1.01 to 2.13). By adding the CBF ratio to the model with the 3 established predictors, the AUC of the receiver operating characteristic curve increased from 0.76 (95% CI, 0.65 to 0.89) to 0.81 (95% CI, 0.71 to 0.91). This trend toward an increased AUC suggests an improved predictive value.

Conclusions—The CBF ratio is an independent predictor for the development of DCI and can contribute to a better identification of patients at high risk for DCI. (Stroke. 2006;37:409-413.)

Key Words: brain ischemia ■ perfusion ■ risk factors ■ subarachnoid hemorrhage

Delayed cerebral ischemia (DCI) is an important cause for death and disability after subarachnoid hemorrhage (SAH) and occurs in approximately one third of the patients with SAH.1 The etiology of DCI is still unclear. Identification of risk factors can contribute to a better understanding of the pathophysiology of DCI and can help in guiding decisions concerning preventive treatment of DCI.

Several studies have shown that clinical condition on admission, amount of extravasated blood, and age are important predictors for the development of DCI.1–3 Because reduced perfusion in the acute stage after SAH is seen more often in patients who later develop DCI,4–6 perfusion disturbances in the acute stage may not only reflect the impact of primary injury caused by the hemorrhage but may also reflect an increased vulnerability of the brain to develop DCI. Perfusion in the acute stage after SAH can, therefore, be another predictor for the development of DCI.

Because perfusion in the acute stage may be reflected by the clinical condition or may be linearly related to the amount of extravasated blood or age, it is uncertain whether information on perfusion gives additional prognostic information to the already well-established predictors for the development of DCI. The purpose of this study was to assess whether brain perfusion can predict for the development of DCI and, if so, whether brain perfusion has additional prognostic value to the established predictors for the development of DCI.

Methods

Patients
We prospectively enrolled a series of patients admitted within 72 hours after SAH to the University Medical Center Utrecht between September 2003 and January 2005. After the diagnosis of SAH was established on the basis of admission noncontrast computed tomography (CT; NCCT), the examination was completed with CT perfusion (CTP) and CT angiography (CTA). Patients who were admitted to the hospital >3 days after SAH were excluded as were patients <18 years of age and patients with nonaneurysmal causes of SAH, including perimesencephalic hemorrhage. The study was

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approved by the medical ethics committee of the University Medical Center, Utrecht.

CTP Technique and Measurements
In our hospital, patients with SAH routinely undergo NCCT and CTA. To perform a CTA, a timing scan is needed to measure the required scan delay. This conventional timing scan was replaced by the CTP scan, which provides the same timing information in addition to the perfusion data. With CTP, quantitative data on cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak (TTP) can be obtained, as well as the delay time required for CTA. The imaging studies were performed on a 16-slice spiral CT scanner (Philips Mx8000 LDT). CTP source data were derived from sequential scans covering a slab of 2.4-cm thickness selected 4 cm above the sella turcica and angled parallel to the meatio-orbital line to contain the upper parts of the lateral ventricles and the basal ganglia. Forty milliliters of nonionic contrast agent (Iopromide, Ultravist, 300 mg iodine/mL, Schering) was injected at a rate of 5 mL/s followed by a 40-mL saline flush at a rate of 5 mL/s. The following parameters were used: 90 kVp, 150 mAs, 8×3 mm collimation, 512×512 matrix, 200 mm field of view, 1 image per 2 seconds during 60 seconds (total 30 images), UB filter, and standard resolution. Data were transferred to a Philips workstation for postprocessing. Regions of interest were drawn in the peripheral (cortical) and deep (basal ganglia) flow territories of the anterior cerebral artery and the middle cerebral artery by 1 of 2 observers blinded for the development of DCI (B.K.V. and I.v.d.S.) resulting in 8 regions of interest per patient. The postprocessing and measurements could be performed within 5 minutes.

Predictors for DCI
The clinical condition on admission was assessed by means of the World Federation of Neurosurgical Surgeons (WFNS) scale, a 5-point scale based on the Glasgow Coma Scale and the presence or absence of focal deficits. The amount of cisternal and ventricular blood on the initial CT was assessed according to the method described by Hijdra et al. In this scale, each of 10 basal cisterns and fissures is graded on a semiquantitative scale according to the amount of extravasated blood ranging from 0 (no blood) to 3 (completely filled with blood). The total amount of subarachnoid blood is calculated by adding the 10 scores and ranges from 0 to 30. The grading of intraventricular blood is constructed in a comparable fashion, and the sum score of ventricular blood ranges from 0 to 12. In a previous study we found that CBF, measured in a semiquantitative manner, showed a good relation with the development of DCI. When assessing CBF by means of ratios, which represent the ratio of CBF values in opposite regions in both hemispheres, the lowest ratio of CBF provided the highest sensitivity (0.75) and specificity (0.93) compared with the other perfusion parameters (CBV, MTT, and TTP; I.v.d.S., M.W., et al, unpublished data, 2005). A lower CBF ratio corresponds to more asymmetry between both hemispheres. We, therefore, used the CBF ratio as a representative predictor for cerebral perfusion.

Outcome Measurement
The outcome event was the occurrence of DCI. Occurrence of DCI was assessed by a neurologist, blinded for the results of the perfusion CT scan. The occurrence of DCI was divided into probable and definite DCI. Probable DCI was defined as a persisting clinical deterioration (ie, decrease in level of consciousness, defined as a drop in the Glasgow Coma sum scale of 1 point), a new focal deficit (eg, hemiparesis, dysphasia, etc), or both with no evidence for rebleeding or hydrocephalus on CT and exclusion of other medical causes, such as infections or metabolic disturbances, but without hypodensity on CT. Definite ischemia was defined as probable ischemia but with confirmation of infarction on follow-up CT. In all of the analyses, the proportion of patients with DCI includes both definite and probable ischemia.

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Analysis
We used descriptive statistics for demographics, amount of cisternal and ventricular blood, treatment strategy (coiling or clipping), and timing for all of the patients. Timing of the intervention was categorized into early (<4 days after the ictus) and postponed (day 4 or later).

Because many patients die in the first days after SAH, the proportion of patients at risk for DCI differs per day. To account for this, we used survival analysis techniques to estimate the relationship between the CBF ratio and DCI. Patients were censored at the day of dying or rebleeding. To visualize the relation between the CBF ratio and DCI, we made Kaplan–Meier plots for the development of DCI according to the CBF ratio (dichotomized at their median range). To obtain crude hazard ratios (HR), which can be interpreted as relative risks, we used the Cox proportional hazards model. In subsequent multivariate analysis, we assessed to what extent the adjusted HR differed from the crude HR. HRs were considered statistically significant if the 95% CI did not include 1. For the survival analysis, age was categorized per 10 years, and the CBF ratio was categorized in deciles. The clinical score (WFNS grade) and the amount of subarachnoid blood (combined sum score of both cisternal and ventricular blood) were used as continuous variables.

The additional prognostic value of the CBF ratio was calculated by comparing 2 multivariate models. The first model contained clinical condition on admission, amount of blood, and age. The second model contained clinical condition on admission, amount of blood, age, and the CBF ratio. All of the variables were used as continuous variables. The discriminative performance of the models was evaluated by constructing receiver operating characteristic (ROC) curves. The more an ROC curve is located in the upper left corner of

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the graph, the higher the sensitivity and specificity for the prediction for development of DCI. An area under the curve (AUC) of >0.75 is considered a good test. The 2 AUCs were calculated and compared. By using the method as described by Delong et al, we corrected for the correlation between the 2 AUCs, because both ROC curves were based on the same population.

Results
We included 75 patients. Evaluation of the CTP scan was not possible in 6 patients because of movement of the patient or insufficient contrast enhancement. Of the 69 remaining patients, 20 developed DCI (16 definite with new hypodensities on follow-up CT, 1 with bilateral hypodensities). Fourteen of the 69 patients died during their clinical course, 5 in the first 3 days after admission. Nine of these 14 patients (13%) died before treatment, but none of them because of DCI. Five patients died after treatment. Three of them were clipped, and 2 were coiled. The reason for their death was DCI in 4 patients and pneumonia combined with congestive heart failure in 1 patient. Table 1 shows the baseline characteristics of all 69 patients. Of the 24 patients treated by endovascular coiling, 6 developed DCI (25%; 95% CI, 12% to 45%), and of the 36 clipped patients, 14 developed DCI (39%; 95% CI, 25% to 55%). Thirteen patients were treated after day 4, of whom 5 were coiled and 8 were clipped (median day 7; range, 4 to 23).

Figure 1 shows the Kaplan–Meier curves for the occurrence of DCI according to high and low CBF ratios. Table 2 shows the univariate (crude) and multivariate (adjusted) HRs of age, clinical condition on admission, amount of blood, and the CBF ratio. In the univariate analysis the HRs of age, clinical condition and CBF ratio were statistically significant.

The CBF ratio and clinical condition remained significant after adjustment for the other predictors. The adjusted HR of CBF ratio in deciles was 0.63; this means that if all other predictors are kept constant, an absolute reduction of 10% in CBF ratio increases the risk for DCI by 37%. The AUC of the ROC curve of the 3 predictors, age, clinical condition on admission, and amount of blood, was 0.76 (95% CI, 0.65 to 0.89), and the AUC of the ROC of the 3 predictors combined with the CBF ratio was 0.81 (95% CI, 0.71 to 0.91; Figure 2). This difference of 0.05 in AUC was not significant (P=0.20). Figures 3 and 4 show an example of a patient with and without perfusion asymmetry who did and did not develop DCI.

Discussion
This study shows that the CBF ratio measured in the acute stage after SAH is a good predictor for the development of
DCI. The lower the CBF ratio (indicating more asymmetry between the perfusion of both hemispheres), the higher the risk of developing DCI. In the univariate (crude) analysis, age, clinical score on admission, and CBF ratio were significant predictors. After adjusting for the other variables, age was no longer statistically significant. Adding the CBF ratio to the model with the 3 established predictors, age, clinical score on admission, and amount of blood, showed a trend toward an increased AUC, which suggests an improved predictive value.

Both clinical condition on admission and the CBF ratio remained independent predictors in the multivariate analysis. The clinical condition, measured by mean of the WFNS score, is mainly a function of the level of consciousness, the latter being a reflection of the global brain perfusion. We used the CBF ratio as a parameter, which provides information on perfusion asymmetry, instead of quantitative global brain perfusion. The use of a CBF ratio, which compares the same regions in opposite hemispheres, may underestimate decreased flow and, thus, the predictive value of this method, because of frequently bilaterally or globally decreased flow and ischemia in acute SAH.

Although the AUC of the ROC curve with the CBF ratio added to the 3 established predictors was higher than that of the ROC curve of the 3 established predictors only, this difference was not statistically significant. The number of patients required to show a significant difference in AUCs to the extent as in our study with a probability of 95% is 495. Thus, the relative small sample size precludes definite conclusions.

For our analysis, we chose the CBF ratio as representative parameter for brain perfusion. We chose this parameter for 2 reasons. First, the CBF is a reflection of both CBV and MTT, because CBF = CBV/MTT (central volume principle) and, second, because we showed that the CBF ratio provided the highest sensitivity and specificity for the development of DCI in a previous study (L.v.d.S., M.W., et al, unpublished data, 2005). CTP provides quantitative information on CBV, CBF, MTT, and TTP, and interpretation of these 4 parameters gives information on functionality of autoregulation. This informa-
tion is valuable, because the development of DCI depends to a great extent on the capacity of cerebral autoregulation. Using the CBF ratio as the only representative for CTP in our analysis, therefore, most likely underestimates the prognostic value of CTP.

Although the relation between CBF reduction or hemodynamic disturbances in the first 3 days after SAH and development of DCI has been reported previously, our study is the first to determine the added prognostic value of brain perfusion to previously identified risk factors in predicting DCI. The interpretation of quantitative perfusion values as measured by CTP has some restrictions. Although the accuracy of CTP has been validated many times in animal and human models, controversies exist to the quantification of CTP has some restrictions. Although the accuracy of CTP has been validated many times in animal and human models, controversies exist to the quantification of CTP. We avoided this problem by analyzing the data in a semiquantitative manner. A disadvantage of this method is that bilateral decreased perfusion can be missed. In future studies, this can be tested by comparing quantitative perfusion values in different flow territories. Another limitation of brain perfusion measurements by means of CTP is the limited brain volume included in the analyses (1 slab of 2.4 cm), which may underestimate the relation between perfusion asymmetry and development of DCI.

Although the CBF ratio as measured with CTP is a good predictor for the development of DCI, and CTP can easily be performed after the NCCT with quick postprocessing and straightforward interpretation, there are a few disadvantages. Despite the fact that the CTP scan replaces the time lapse, the patient is exposed to additional dose and contrast material compared with the conventional time lapse. Also, a 5-minute delay before performing the CTA scan is required to keep venous enhancement to a minimum. Therefore, implementation of CTP in the clinical practice should be considered only if it has clinical consequences or guides treatment decisions. A pilot study on the prophylactic use of transluminal balloon angioplasty in patients with SAH suggested an important risk reduction for the development of DCI. A phase II study addressing efficacy of this treatment is under way. If this treatment reduces the risk of DCI, CTP might be a good tool to select patients for this therapy.

Acknowledgments
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References
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