Delayed cerebral ischemia (DCI) occurs in approximately 20% to 30% of patients with aneurysmal subarachnoid hemorrhage (SAH) and is a major cause of death and disability in these patients.1–5 Despite many years of research, the pathogenesis of DCI is still not clarified.6 Identification of risk factors may contribute to a better understanding of the pathogenesis of DCI and may improve prevention and treatment. Several studies7–12 have shown that a poor clinical condition on admission and a large amount of extravasated blood increase the risk of DCI. We studied 2 additional baseline characteristics to assess their prognostic value for the development of DCI after SAH: first, the duration of initial loss of consciousness after the hemorrhage, because this might reflect the severity of the initial ischemia caused by a reduced perfusion pressure during aneurysmal rupture,13 which could be related to later development of DCI; and second, the presence of 3 main risk factors for atherosclerotic disease (smoking, hypertension, and previous history of stroke or myocardial infarction), because preexistent atherosclerotic lesions might explain the often multifocal localizations of DCI. To adjust our data for the known risk factors, we incorporated the clinical condition on admission and the amount of extravasated blood in our analyses.

Subjects and Methods

We prospectively studied a consecutive series of 125 patients with SAH who were admitted to the University Hospital Utrecht between January 1995 and July 1996. Only patients who were admitted within 4 days after the hemorrhage were included in the study. The diagnosis of SAH was made by the presence of extravasated blood in the basal cisterns on CT, or if CT was negative, by xanthochromia of the cerebrospinal fluid.14 Patients with nonaneurysmal perimesencephalic hemorrhage15 were excluded, as were patients with other nonaneurysmal causes for the SAH. Conventional and/or CT angiography was performed in 107 patients; the remaining 18 patients died before angiography could be performed. We included these patients because the distribution of hemorrhage on the CT scan strongly suggested an aneurysmal origin; in 6 of these the aneurysm was confirmed by postmortem examination.

The clinical condition on admission was assessed by means of the World Federation of Neurological Surgeons (WFNS) scale, a 5-point scale based on the Glasgow Coma Scale and the presence or absence of focal deficits.16 A dichotomy was made between good (WFNS I, II, and III) and poor (WFNS IV and V) neurological condition on admission.

All patients were kept under continuous observation for at least 2 weeks of their hospitalization and were treated according to a standardized protocol, which consisted of absolute bedrest, oral nimodipine treatment, refraining from antihypertensive medication, and intravenous administration of fluid until a positive fluid balance of at least 750 cc was achieved. Early surgery (within 4 days after the hemorrhage) was attempted if the WFNS condition was poor or in patients with a large amount of extravasated blood on CT, or if the patients were rapidly deteriorating.

Received March 15, 1999; accepted July 19, 1999.
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hemorrhage) was performed in 45 patients who were either in a very good condition on admission (WFNS score I or II) or required acute surgical intervention because of an early rebleed, presence of a large hematoma, or severe hydrocephalus. In 46 other patients, clipping of the aneurysm was postponed until at least 10 days after the hemorrhage; 34 patients did not undergo surgery. All patients received standard hypervolemic normotensive treatment when DCI was suspected.

One of the authors (J.W.H.) personally interviewed the patients during the initial days of hospitalization, always in the presence of a proxy or other eyewitness of the event. In patients whose condition did not allow a personal interview (n=40), data about the duration of unconsciousness and previous history were obtained from a proxy only, with verification from the medical records. Data from patients who died soon after admission (n=18) were obtained from the medical records only.

In all patients we recorded the duration of loss of consciousness for the SAH leading to hospital admission and for any subsequent rebleed. Loss of consciousness out of hospital was considered present if the eyewitness reported in the interview that “no purposeful response to verbal or physical stimulation” had occurred. Because an exact assessment of duration of unconsciousness may not always be reliable, we applied easily distinguishable categories: (1) no loss of consciousness, (2) <1 hour, (3) between 1 and 24 hours, and (4) ≥ 24 hours. For the analyses we dichotomized the duration of unconsciousness at 1 hour to discriminate between less-severe and more-severe impact of the hemorrhage. An additional analysis on any duration of unconsciousness versus no loss of consciousness was performed. In 2 patients the duration of unconsciousness could not be assessed because they were alone at the time of the hemorrhage; both were found in a confused state by others. These 2 patients were excluded from all analyses.

For every patient we recorded the following additional items: history of hypertension (diastolic blood pressure >95 mm Hg on at least 2 occasions, or medical treatment), history of myocardial infarction or stroke, and former or current smoking. Additionally, we asked whether patients had used any salicylates within 2 weeks before the bleed, because this might possibly protect against DCI.17

We assessed the amount of cisternal blood on the initial CT scan according to the method described by Hijdra et al.18 Patients in whom the initial CT was performed more than 2 days after the hemorrhage (n=11) or whose initial CT scan could not be retrieved from the referring hospital (n=6) were excluded from this part of the assessment. The sum scores of blood in the subarachnoid space were dichotomized at their median value (23). We quantified the size of the frontal horns by means of the bicaudate index (BCI). To calculate age-adjusted relative sizes, the BCIs were divided by the corresponding upper limit per age group.19 Hydrocephalus was defined as an age-adjusted relative BCI of >1.

The primary outcome event was the occurrence of DCI, which was divided into probable and definite DCI. Probable ischemia was defined as a gradual decline in the level of consciousness or a gradual development of new focal deficits or both, with no evidence for a rebleed or hydrocephalus on CT, and exclusion of other medical causes, but without hypodensity on CT scan. Definite ischemia was defined as probable ischemia, but with confirmation of infarction on CT or autopsy. In all analyses, the proportion of patients with DCI includes both definite and probable ischemia. Other outcome events were rebleeding, defined as a sudden clinical deterioration with evidence of new blood on CT in comparison with a previous scan, and death from all causes. The recording of outcome events ended 3 months after admission.

Data Analyses

Because many patients die in the first days after the hemorrhage, the proportion of patients at risk for DCI differs per day. Moreover, the risk of dying might be related to the variables of interest. To exclude the patients who die early in the analyses, we used survival analysis techniques in which we censored deaths: we compared the occurrence of the primary outcome event (DCI) for all selected baseline characteristics by means of the Cox proportional hazards model, which yielded a crude hazard ratio (HR). In subsequent multivariate analyses we assessed to which extent adjusted HRs in patients with short or no unconsciousness compared with patients who were unconscious for >1 hour differed from the crude HR. HRs may be interpreted as relative risks20; they were considered statistically significant (P<0.05) if the 95% CI did not include 1.

Because rebleeding generally induces a new episode of loss of consciousness, with a subsequently altered risk of DCI, we performed 2 analyses: in the first analysis, the occurrence of DCI was related to the duration of unconsciousness from the hemorrhage leading to hospital admission. A time window of 24 hours was applied in the assessment of the duration of loss of consciousness; eg, in a patient who deteriorated within the first 24 hours after the hemorrhage, the longest episode of loss of consciousness was recorded. Any deterioration after 24 hours was considered a separate outcome event. Patients were censored in case of rebleeding or death from all causes. In the second analysis, which incorporated rebleeding, the longest episode of loss of consciousness was recorded and set at t=0 (left truncation), with the occurrence of DCI as primary outcome event and with censoring only for death from all causes.

Results

Forty of the 125 (32%) patients who fulfilled the inclusion criteria died during their clinical course, 14 within the first day after admission. Thirty-nine patients (31%) developed DCI, 34 definite and 5 probable. In 20 of these patients the ischemic symptoms developed after operation.

The Table shows the occurrence of DCI, based on the hemorrhage on admission, in relation to the baseline charac-
A poor WFNS grade on admission, duration of unconsciousness of >1 hour, and a large amount of blood in the subarachnoid space were significantly related to the presence of DCI in the univariate analysis. The crude HR associated with unconsciousness >1 hour was 6.0 (95% CI 3.0 to 12.0) in the first analysis (based on the hemorrhage on admission) and 5.7 (95% CI 2.8 to 11.6) in the second (based on the hemorrhage with the longest duration of unconsciousness in case of a rebleed). Because both analyses yielded similar results, all data refer to the first type of analysis.

We found no significant influence of sex, age, smoking, hypertension, history of stroke or myocardial infarction, or recent use of aspirin. The HR for the presence of any risk factor for atherosclerotic disease (smoking or history of hypertension, stroke, or myocardial infarction) versus none of these risk factors was 1.4 (95% CI 0.6 to 3.5); the HR for any duration of unconsciousness versus no loss of consciousness was 3.3 (95% CI 1.3 to 8.5).

The HR for duration of unconsciousness remained essentially the same after adjustment for sex, age, WFNS grade on admission, amount of blood in the subarachnoid space, timing of surgery, presence of risk factors for atherosclerosis, and recent use of aspirin. Stepwise introduction of the univariately significant variables into the multivariate model resulted in statistical significance for the duration of unconsciousness and the sum score of subarachnoid blood only.

The Figure shows the Kaplan-Meier curves for the occurrence of DCI according to duration of unconsciousness.

**Discussion**

The duration of unconsciousness after the very moment of a SAH proved to be a strong predictor for the occurrence of DCI. Patients who lose consciousness for >1 hour at the time of the hemorrhage have a 6-fold increased risk for the development of DCI compared with those who lose consciousness for <1 hour or who remain fully awake at the time of the hemorrhage. This increased risk is of the same magnitude when episodes of rebleeding are taken into account. The prognostic value of the duration of unconsciousness for the development of DCI is stronger than that of previously identified risk factors, such as the neurological condition on admission and the amount of cisternal blood on CT. This might be explained by the fact that both neurological condition and amount of blood in the subarachnoid space change over time and thus depend on the time interval between onset of SAH and admission, whereas the duration of unconsciousness after the SAH is an unchanging characteristic. Because the duration of loss of consciousness on the one hand and neurological grade on admission and amount of subarachnoid blood on the other are related, adjustment for these risk factors did not essentially alter the results.

The loss of consciousness at the time of the hemorrhage is caused by global ischemia, resulting from a lack of perfusion pressure during aneurysmal rupture. The duration of loss of consciousness might reflect the severity of this perfusion deficits and global ischemia. Our data suggest that the severity of the initial ischemia is an important pathogenetic factor in the development of DCI. Elucidation of the underlying pathophysiological mechanism requires further study.

We did not find an increased risk for DCI in the presence of risk factors for atherosclerosis. In a recent study, cigarette smoking was found to increase the risk of symptomatic vasospasm after aneurysmal SAH. Our study could not support this finding to a significant degree.

The use of salicylates in the 2-week period before admission did not alter the risk for DCI. Increased platelet aggregability might play a role in the pathogenesis of DCI. An observational study has shown that patients who had taken
aspirin prior to their hemorrhage had a relatively low risk for ischemic symptoms and ischemic lesions on CT. 17 That study was based on the presence of salicylates in urine samples on admission, whereas in our study the use of salicylates was not well documented in the medical records and the information obtained from relatives on use of salicylates may have been unreliable.

We did not investigate other factors that might be related to the occurrence of DCI, such as factors related to the surgical procedure, because these are difficult to quantify.

One might question the reliability of the assessment of duration of unconsciousness by patients and proxies. Indeed an assessment of the exact duration may be difficult to make. During the personal interview, most patients and all proxies remembered in detail the circumstances under which the SAH occurred, the presenting symptoms, and the subsequent activities. A distinction between the presence or absence of unconsciousness and between the duration of unconsciousness for less than or more than 1 hour was never difficult to make.

Another limitation of our study is that for 18 patients who died soon after admission, we did not personally interview a proxy or eyewitness. Data on possible risk factors in these patients were often lacking in the medical records; a dichotomy in duration of unconsciousness at 1 hour could reliably be made.

The duration of unconsciousness is a very important risk factor for the development of DCI. This finding may provide new insights into the pathogenesis of DCI and may lead to increased attention for patients at high risk of delayed ischemia.

References
Initial Loss of Consciousness and Risk of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

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Stroke. 1999;30:2268-2271
doi: 10.1161/01.STR.30.11.2268

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