Infarction After Aneurysm Rupture Does Not Depend on Distribution or Clearance Rate of Blood

P.J.A.M. Brouwers, MD; E.F.M. Wijdicks, MD; and J. Van Gijn, MD

Background and Purpose: We sought to determine the contribution of the amount, distribution, and clearance rate of extravasated blood in relation to occurrence of infarction and outcome in patients with aneurysmal subarachnoid hemorrhage.

Methods: We prospectively studied 59 consecutive patients with aneurysmal subarachnoid hemorrhage admitted within 72 hours by means of serial computed tomographic scanning, close clinical observation, and assessment of outcome after 3 months.

Results: Infarction occurred in 17 of the 59 patients. The arterial territories involved hardly reflected the distribution of subarachnoid blood in the basal cisterns on computed tomography, and even the side of the infarcts corresponded only weakly with the side on which most extravasated blood was seen. Infarction occurred twice as often in patients with large amounts of subarachnoid blood; this difference was not significant on its own but is in agreement with previous studies. A low clearance rate of cisternal blood was not related to the occurrence of infarction; a relation between clearance rate and poor outcome was largely explained by the amount of subarachnoid blood on the initial computed tomogram and by a low Glasgow Coma Scale score on admission.

Conclusions: The fact that infarction is related to the total amount but not to the distribution or clearance rate of extravasated blood argues against a direct role of extravasated blood and in favor of systemic factors, dependent on the severity of the initial hemorrhage. (Stroke 1992;23:374-379)

KEY WORDS • cerebral infarction • subarachnoid hemorrhage • tomography, x-ray computed

It has been estimated that of all subarachnoid hemorrhage (SAH) patients, approximately one third will deteriorate in hospital, mainly as a result of infarction, rebleeding, or hydrocephalus.1-8 Early prediction of risk for each of these complications is important in the management of patients and in the evaluation of new treatments.

The Glasgow Coma Scale score is a well-established predictor of outcome.2-9,10 Recently some other predictive factors have been identified, including the total amount of subarachnoid blood,10,11 the presence of thick blood clots,12-18 hyponatremia,19 and abnormalities on the electrocardiogram.20 With regard to the amount of extravasated blood as a predictive factor for infarction and poor outcome, all studies have used the computed tomographic (CT) scan on admission.

Some studies have examined the rate at which the blood disappeared from the scan, but mainly to establish the sensitivity of CT as a function of time.21-24 The clearance rate of extravasated blood as a possible predictor of infarction and outcome has not yet been studied. Products released from disintegrated erythrocytes are believed to play an important role in the development of infarction.25,26 Nevertheless, not all patients with large amounts of blood on their initial CT develop infarcts. Perhaps this can be explained by a difference in the clearance rate or the distribution of aneurysmal blood. We investigated this possibility in a prospective series of patients with aneurysmal SAH by means of serial CT, close clinical observation, and standard assessment of outcome.

Subjects and Methods

Between June 1986 and March 1989, we prospectively studied a series of 76 consecutive patients who had symptoms, signs, and CT evidence of aneurysmal SAH. All 76 patients were admitted within 72 hours of the presenting hemorrhage and, after informed consent, were enrolled in the study. Seventeen of the 76 patients were subsequently excluded from the study because of a negative angiogram (11), an arteriovenous malformation (two), or other nonaneurysmal sources of hemorrhage (four). Of the 59 remaining patients, angiography or autopsy demonstrated an aneurysm in 44 (75%). In the other 15 patients, angiography and surgery were not considered because of advanced age (>70 years) or impaired level of consciousness; nevertheless, a ruptured aneurysm was considered highly probable in these patients by typical CT findings alone.27,28 The first 21 of the 59 patients were treated with tranexamic acid, 6 g/day i.v. for 4 days, as part of a separate study regarding rebleeding in SAH.29 All patients were given fluids in a volume of at least 3
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Subarachnoid blood in paired basal cisterns was calculated for each side and compared. A hemorrhage was classified as right or left when a difference of more than 1 point was found, and as symmetric when no such difference existed. Sides of infarction were classified as left, right, or bilateral when ischemic lesions were demonstrated in the left, right, or in both hemispheres, respectively.

For statistical analysis, the \( \chi^2 \) test was used. Probability values were calculated by two-sided tests. The effect of potentially confounding variables and the predictive value of the significant variables in combination were studied with a stepwise logistic regression method (Statistical Package for the Social Sciences). For these analyses all possible determinants of infarction and outcome with more than two categories were dichotomized (Glasgow Coma Scale score on admission: normal \([14]\) versus decreased level of consciousness \(<14\); time of first CT scan: 0–24 hours versus 25–72 hours; subarachnoid blood sum score on initial CT: \(>20\) versus \(\leq20\); relative clearance rate per day of cisternal blood: \(>19\)% versus \(\leq19\)% [median value, 19%]; and Glasgow Outcome Scale: poor outcome [death/persistent vegetative state/severe disability] versus good outcome [moderate disability/good recovery]).

Results

In the 59 patients, 192 CT scans were performed during the first 4 weeks, until operation (aneurysm clipping), rebleeding, or death. All patients showed extravasated blood in the subarachnoid cisterns or fissures. After 1 week, subarachnoid blood was no longer visible in 50% of the scans in patients who had not died, rebled, or been operated on, and after 9 days all scans of the remaining patients were without subarachnoid blood. A hematoma was present on the initial CT in 20 of the 59 patients. These hematomas were usually intraparenchymal (16), less often in the cavum septi pellucidi (3) or in the subdural space (one), and disappeared between days 10 and 14.

Admission CT was obtained within 24 hours in 41 patients (median sum score of cisternal blood, 21; range 1–30), within 24–48 hours in 14 (median 16; range 4–28), and within 48–72 hours after SAH in four patients (median 5.5; range 2–7). Figures 1 and 2 show the amount of subarachnoid blood on first and second CT for every patient with and without infarction, respectively. These two figures demonstrate a large variation between individual patients, and a relation with infarction does not emerge.

The clearance rate per day of cisternal blood could be calculated in 53 of the 59 patients who had a second CT before rebleeding, surgery, or death. In 46 of the 53 patients (87%), this second scan was performed within 4 days after SAH. The median value of the relative clearance rate of cisternal blood per day was 19% (range 0–100%). The clearance rates of patients with and without infarction were not significantly different (median 18%, range 0–100%; median 19%, range 0–79%, respectively, Figure 3). With regard to the time of the first CT, there was no significant difference between clearance rate values of patients with the first scan made within 24 hours and those in whom the first scan was made after 24–72 hours (median 17%, range 0–100%; median 28%, range 7–79%, respectively).

Possibly predictive factors for infarction and outcome in general are listed in Table 1: the Glasgow Coma Scale score on admission, the time of the first CT, the amount of subarachnoid blood on the first CT, the presence of a hematoma on the initial CT, and the relative clearance rate per day of cisternal blood. A Glasgow Coma Scale score of <14 points, a large amount of subarachnoid

During the study period, which lasted until all evidence of extravasated blood on CT had disappeared or until rebleeding, aneurysm surgery, or death, all 59 patients were under close observation in an intensive-care or high-dependency unit. Thirty-eight patients underwent aneurysm surgery at approximately 12 days after the presenting hemorrhage.

The level of consciousness on admission was graded according to the Glasgow Coma Scale.\(^{33}\) Computed tomographic scanning was performed on admission and repeated every 2 or 3 days until complete disappearance of extravasated blood, or in the meantime when the patient’s condition deteriorated. The amount of cisternal blood on CT was separately graded from 0 to 3 points for 10 different cisterns and fissures. The sum score was obtained by summation of each cisternal score (0–30 points).\(^{34}\) Intracerebral hematoma was graded as present or absent. The scans were judged by two observers together, who were blinded to the clinical outcome.

In choosing a measure for the clearance rate of subarachnoid blood, we formulated the following criteria. First, the measurement should be limited to the first few days after SAH and admission. Predictive factors have little value if they can be established only after a week or more. Moreover, the adverse effect of short-term treatment with antifibrinolytic agents, with regard to the occurrence of infarction,\(^{29}\) suggests that the factors eventually leading to infarction are already active in the first few days. Second, the clearance rate should be expressed as an average per day. Although such a method obscures possible differences in clearance rate between, for instance, day 1 and day 3 after SAH, it solves the problem that it is often impossible to obtain a second scan at a precise moment after the first one for medical as well as practical reasons. Third, allowance should be made for patients with little blood on the first CT, who can show little clearance in absolute terms. We therefore used a relative clearance rate. In this way the relative clearance rate per day of cisternal blood (sum score) over the first two CT scans was calculated, on the condition that the first scan showed blood and the second scan was obtained before rebleeding or aneurysm surgery occurred. In formula:

\[
\text{Sum score CT}\left(1\right) - \text{sum score CT}\left(2\right)
\]

\[
\times 100 / \left[ \text{day CT}\left(2\right) - \text{day CT}\left(1\right) \right]
\]

Infarction was defined using previously described criteria.\(^{35}\) Outcome was assessed at 3 months according to the Glasgow Outcome Scale\(^{36}\) by neurologists who were unaware of CT findings.

The relation between the distribution of subarachnoid blood on admission and the side of the infarct on a later scan or at autopsy was also studied. The amount of subarachnoid blood in paired basal cisterns was calculated for each side and compared. A hemorrhage was classified as right or left when a difference of more than 1 point was found, and as symmetric when no such difference existed. Sides of infarction were classified as left, right, or bilateral when ischemic lesions were demonstrated in the left, right, or in both hemispheres, respectively.\(^{19}\)

I/day\(^{9,30,34}\) and received no antihypertensive drugs.\(^{31,32}\)
stroke (>20), the presence of a hematoma, or a low relative clearance rate per day for cisternal blood (≤19%) were all significantly related to poor outcome (p<0.001, p<0.001, p<0.01, and p<0.025, respectively), but not specifically to infarction. Patients with a large amount of subarachnoid blood (>20) on admission CT had twice as many infarcts, but this difference did not reach statistical significance. The time of the initial scan was not significantly associated with any outcome characteristics, although patients who were admitted later tended to have a better outcome.

A low relative clearance rate per day of cisternal blood (≤19%) was not related to any of the following variables: the use of tranexamic acid, a large amount of subarachnoid blood (>20), a hematoma, or the time of first CT. In contrast, it was strongly related to a Glasgow Coma Scale score on admission of <14 points (p<0.001). The Glasgow Coma Scale score on admission, in turn, was significantly related to the presence of a hematoma (p<0.025) but not to the use of tranexamic acid, a large amount of subarachnoid blood (>20), or the time of first CT. This prompted us to correct for the confounding effects between these baseline variables.

A stepwise logistic regression analysis on Glasgow Coma Scale score, timing of first CT, amount of subarachnoid blood, presence of a hematoma, use of tranexamic acid, and clearance rate of subarachnoid blood with poor outcome as the dependent variable resulted in a model in which a cisternal blood score of >20 was the most significant independent predictive variable (p=0.0005), followed by a Glasgow Coma Scale score of <14 (p=0.0157). In this model to predict the chance of poor outcome, neither a low relative clearance rate per day of cisternal blood nor the presence of a hematoma reached statistical significance, since the confounding effects of a subarachnoid blood score >20 and a Glasgow Coma Scale score of <14 were too strong. In a stepwise logistic regression analysis with infarction as the dependent variable, none of these baseline characteristics reached the level of significance.

Seventeen of the 59 patients (29%) developed an infarct in one or more vascular territories (nine and eight patients, respectively). In all cases the clinical diagnosis was confirmed by the presence of radiolucent lesions on CT. These lesions on CT were permanent in
TABLE 1. Baseline Characteristics Related to Infarction and Outcome

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Total No. of patients</th>
<th>Infarction</th>
<th>Outcome (Glasgow Outcome Scale score)</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Total No. of patients</td>
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<td>42</td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
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<tr>
<td>&lt;14</td>
<td>28</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>31</td>
<td>10</td>
<td>21</td>
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<td>Time of first CT scan</td>
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<tr>
<td>0–24 hr</td>
<td>41</td>
<td>12</td>
<td>29</td>
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<tr>
<td>25–72 hr</td>
<td>18</td>
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<td>Subarachnoid blood sum score</td>
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<td>&gt;20</td>
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<td>Hematoma</td>
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<td>6</td>
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</tr>
<tr>
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<td>39</td>
<td>11</td>
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<tr>
<td>Total No. of patients</td>
<td>53‡</td>
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<td>37</td>
</tr>
<tr>
<td>Clearance rate of subarachnoid blood</td>
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</tr>
<tr>
<td>&gt;19%</td>
<td>25</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>≤19%</td>
<td>28</td>
<td>9</td>
<td>19</td>
</tr>
</tbody>
</table>

CT, computed tomographic.  
*p < 0.001, †p < 0.01, ‡p < 0.025 by χ² test.  
‡53/59 patients with cisternal blood present and two CT scans before rebleeding or operation.

14 patients and transient in three. Of the 17 patients with infarction, only three had been treated with tranexamic acid. In 10 of the 17 patients with infarction, angiography had been performed at approximately day 10 after SAH. Seven patients did not show vasospasm and three patients showed focal vasospasm in the arterial segments around the aneurysm.

Figure 4 shows a clear correlation between aneurysm site and the location of the subsequent infarct (nine of 10 known aneurysms). In contrast, there was no relation between the distribution of the basal cisterns that were completely filled with blood on the initial CT and the location of the subsequent infarct. Even the side on which the subarachnoid blood predominated on the first or on the second scan did not correspond with the side of the infarct (Table 2). Finally, if we restricted the sum score for subarachnoid blood to the five "central" cisterns (interhemispheric fissure, suprasellar cisterns, and basal parts of the Sylvian cisterns), regardless of the side, this central sum score was still not significantly related to infarction. The relative clearance rates per day for these central sum scores alone also showed no relation with infarction.

Discussion

Our main findings are twofold. First, the amount of extravasated blood on initial CT strongly predicts poor outcome but not specifically infarction, and the distribution of the blood in the basal cisterns was hardly, if at all, related to the vascular territory involved in infarction. Second, a low relative clearance rate of cisternal blood is not related to infarction; there is some association with poor outcome, but this relation is strongly dependent on the amount of subarachnoid blood on the initial scan and the level of consciousness on admission.

All 59 patients had signs of subarachnoid blood on the initial CT, which was obtained within 72 hours after SAH. After 9 days all evidence of subarachnoid blood had disappeared from the scans of surviving patients. Evidence of a hematoma on CT disappeared rather quickly between days 10 and 14. This confirms earlier findings and again proves the sensitivity of CT in visualizing extravasated blood after SAH.

None of the entry variables in our study, including the amount of subarachnoid blood, was significantly related to infarction. In contrast, a relation between the initial amount of subarachnoid blood on CT and clinical signs of infarction has been demonstrated previously by several investigators. In the study of Hijdra et al, who used the same CT grading method and who introduced the full range of subarachnoid blood scores in the prediction model, only 14 (8%) of the 176 patients had >20 points of subarachnoid blood (maximum 30), in contrast to 25 of 59 patients (42%) in the present study. This difference might be explained, at least in part, by improved resolution of CT scanners in the meantime. The most important difference between the two studies may be the smaller number of patients in our current series; patients with >20 points of subarachnoid blood had twice as many infarcts (Table 1), but this did not reach statistical significance on its own.

Products of disintegrating blood clots are believed to play a role in infarction, and therefore the time during which these clots are present might be considered an important factor. As a measure for the clearance rate of subarachnoid blood we defined the propor-
The functional decrease of the total amount of extravasated blood over the first few days, expressed as an average per day. A low clearance rate, below the median value, was significantly related to poor outcome but not to infarction. However, a low clearance rate was dependent on two other factors that had been identified previously15: a large amount of subarachnoid blood on the initial scan and a depressed level of consciousness on admission. These two associations do not necessarily represent direct causes of disease but may merely reflect the impact of the aneurysmal rupture on the brain, which perhaps determines outcome in a more direct fashion.

Our study of the clearance rate of subarachnoid blood is limited by the fact that blood can be identified by CT only if it still contains iron and by differences in timing of the first and subsequent scans. Clearance of subarachnoid blood probably starts immediately after SAH. Indeed, the 18 patients with a late initial CT (25–72 hours) had significantly lower sum scores of subarachnoid blood (p<0.05), but this time interval was not significantly related to any of the other baseline characteristics nor to infarction or outcome. Our assumption of a linear clearance rate of subarachnoid blood over the first few days after SAH is indirectly supported by the similarity in clearance rates between patients with an early or a late initial CT. A high level of antifibrinolytic activity in the cerebrospinal fluid after the SAH is probably not a determinant of the clearance rate because this reflects a damaged blood–cerebrospinal fluid barrier rather than increased fibrinolysis.37

Because our method of sum scores obscures the possible importance of localized accumulations of blood in the basal cisterns ("severe significant clot or thick layer of subarachnoid blood"),17 we separately analyzed the sum scores for the five central cisterns that contain the circle of Willis. It has also been suggested that patients with a combination of clots in the stem of the Sylvian fissure and in the basal interhemispheric fissure are more likely to develop severe vasospasm in both the proximal parts of the middle cerebral artery and the anterior cerebral artery.17 We therefore analyzed the relation between the distribution of the basal cisterns completely filled with blood and the location of the infarct (Figure 4). However, we were not able to reproduce the previous finding of Kistler et al17 of a relation between the distribution of the subarachnoid blood and the arterial territory of the ischemic lesion. The side on which most subarachnoid blood was found on admission corresponded with the side of the subsequent infarct in only nine of the 17 patients (53%) (Table 2). On the second scan the sides corresponded in only five patients (29%). These discrepancies confirm similar findings by Hijdra et al.15 Moreover, if we calculated the relative clearance rate per day for the central subarachnoid cisterns, there was again no relation with subsequent infarction.

In conclusion, there are several reasons to believe that the predictive value of "large localized clots" for infarc-
tion has been overestimated. Our results confirm that infarction is the result of a multifocal or diffuse process.\textsuperscript{38,39} A recent study comparing nonaneurysmal (perimesencephalic) hemorrhage and aneurysmal hemorrhage found that infarction occurred only in patients with aneurysms, despite similar amounts of subarachnoid blood.\textsuperscript{40} That the source and the total amount of extravasated blood but not its distribution or clearance rate is related to infarction may suggest that vasospasm and hyperfusion after aneurysm rupture are not directly caused by the extravasated blood itself, but by vascular and systemic reactions to the rupture of an artery.

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Infarction after aneurysm rupture does not depend on distribution or clearance rate of blood.
P J Brouwers, E F Wijdicks and J Van Gijn

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