ACUTE SUBDURAL HEMATOMA (SDH) IS ONE OF THE LEADING CAUSES OF DEATH AND DISABILITY IN SEVERE TRAUMATIC BRAIN INJURY (TBI).

The physiological findings in the hyperacute phase before evacuation have been described at various times and seem to be affected by low...
cerebral blood flow (CBF) values (50) and low cerebral perfusion pressure (CPP) associated with elevated intracranial pressure (ICP) (59). This is one of the reasons for the high mortality rate in the ultra-early acute phase, as well as for the cortical swelling observed in surviving patients. Because SDH is a neurosurgical emergency, prolonging the diagnostic monitoring conflicts with the need for urgent evacuation. Conversely, the evaluation of the physiological response occurring in the brain region located beneath the SDH after evacuation could be potentially useful for targeting treatment during the postoperative phase.

Several abnormalities, such as hyperglycolysis, have previously been demonstrated in the cortex beneath the evacuated SDH by using positron emission tomographic (PET) techniques (4). In the same area, microdialysis and studies on the partial pressure of tissue O2 have recently shown the presence of a decrease in brain tissue O2 tension and an increase in lactate and pyruvate levels (24). However, perfusion disturbances of the brain tissue located under the SDH remain to be investigated, particularly after evacuation, as there are very few studies that focus on this aspect, and these studies show contradictory results. In fact, although either low or high regional CBF (rCBF) values have been found after SDH removal in 2 previous reports (4, 46), a reversal of the initial reduction in rCBF levels after SDH evacuation has been detected in another isolated investigation (50). These divergent findings suggest that CBF levels in brain tissue underlying an evacuated SDH may be affected in various ways. Furthermore, previous studies did not analyze the time course of CBF values in this region nor their relationships with patient outcome. Consequently, the aim of this study was to analyze CBF values measured in the cortex located beneath an evacuated acute SDH by means of a xenon-computed tomographic (Xe-CT) technique, their time course, and their association with final patient neurological outcome.

PATIENTS AND METHODS

From 2000 to 2005, 676 TBI patients were admitted to the Intensive Care Unit of the Bufalini Hospital, Cesena, Italy; 222 patients (32.8%) were affected by moderate TBI (Glasgow Coma Scale [GCS] score, 9–13) (43, 55), and 454 patients (67.2%) had severe TBI (GCS, 3–8) (43). GCS scores were determined after patients were stabilized (56). Of these TBI patients, 263 patients were found to have an SDH, which was the predominant lesion in 178 cases. Exclusion criteria from Xe-CT studies were the presence of: 1) acute non-evacuated intracranial masses with nonresponsive pupil dilation or rapidly progressive and refractory increase of ICP; 2) early postinjury instability owing to severe multiple injuries; and 3) a fraction of inspired O2 of more than 55% to 60% (60). Consequently, only 72 patients with SDH were submitted to at least 1 Xe-CT examination. Among this series of patients, we selected and retrospectively investigated only those affected by SDH without any satellite contusions and without areas of hypotension, potentially attributable to macrovascular hypoperfusion, in the underlying cortex on conventional CT scans obtained during the Xe-CT study. Therefore, the case material of our study includes 20 patients (19 with severe TBI) with an evacuated SDH who underwent 55 Xe-CT studies. As a control group, we selected 38 Xe-CT studies from 23 patients, 12 of whom (10 with severe TBI) had diffuse lesions (diffuse injury type I, II, III, and IV, according to Marshall et al. [39]), and 11 of whom (9 with severe TBI) had an evacuated isolated extradural hematoma (EDH).

The protocol of centralization of TBI patients in our trauma center has been described in 2 previous articles (52, 53). After admission, in the early phase, the patients with SDH promptly underwent operations. In each of these patients, the bone flap was not repositioned at the end of surgery; in accordance with local neurosurgical protocol. Conversely, in all patients with EDH, the bone flap was repositioned at the end of surgical evacuation, and no patient with diffuse injury underwent a decompressive craniotomy. All patients, except 1 patient with EDH, underwent ICP monitoring and were managed in our Intensive Care Unit using a local staircase protocol to maintain ICP below 20 mm Hg and CPP above 60 to 70 mm Hg, which was illustrated in detail in our previous article (9). For convenience, the steps of treatment were categorized in 3 progressively ascending therapeutic intensity levels of treatment: standard, reinforced, and extreme (9).

CBF Measurement and Analysis

CBF studies were conducted using a CT scanner (Picker 5000; Picker Medical Imaging, Cleveland, OH) equipped for Xe-CT CBF imaging (Xenon CT System-2; Diversified Diagnostic Products, Inc., Houston, TX). Details were reported in our previous studies (7, 8). During postprocessing image analysis, we selected the slice corresponding to the largest SDH fronto-occipital diameter as identified on the CT scan obtained before surgical evacuation. Multiple circular regions of interest (ROIs), wider than 200 mm² (65), were manually drawn on the CT scan in the cortex underlying the evacuated SDH and, symmetrically, in the corresponding contralateral, apparently normal cortical mantle (Fig. 1). In each ROI, CBF values were calculated using special software (Xe-CT System, Version 1.0 w; Diversified Diagnostic Products, Inc.). In each patient, CBF data obtained from the ROIs positioned in both evacuated SDH and contralateral hemispheres were separately summarized and expressed as rCBFmean, rCBFmax, and rCBFmin, respectively: rCBFmean represented the mean of all rCBF values of ROIs placed in each hemisphere, whereas rCBFmax was the highest level and rCBFmin was the lowest level of rCBF measured in all ROIs located in each hemisphere. In this way, a single average value was obtained for rCBFmean, rCBFmax, and rCBFmin in each hemisphere. In this setting, to allow comparison with previous studies, CBF values were classified according to the following already reported threshold values (28–30, 44): severe ischemia (CBF <6 mL/100 g/min), moderate ischemia (CBF ≥6 and <18 mL/100 g/min), reduced flow (CBF ≥18 and <33.9 mL/100 g/min), relative hyperemia (CBF ≥33.9 and <55.3 mL/100 g/min), and absolute hyperemia (CBF ≥55.3 mL/100 g/min).

In addition, in each patient, the side-to-side differences in hemispherical rCBFmean, rCBFmax, and rCBFmin were recorded. More precisely, the differences between rCBFmean, rCBFmax, and rCBFmin levels measured in the evacuated SDH hemisphere and those measured in the contralateral hemisphere were calculated and expressed as ΔrCBFmean, ΔrCBFmax, and ΔrCBFmin, respectively. If the rCBFmean, rCBFmax, and rCBFmin values were evaluated at 4 different time intervals: 1) within 24 hours; 2) between 24 and 96 hours; 3) between 4 and 7 days; and 4) after the seventh day postinjury. This temporal categorization was chosen on the basis of previous reports (1, 8, 37, 40, 54).

The same multiple circular cortical ROIs approach was applied in control patients with diffuse injury and EDH. In the case of diffuse injury, in which the discrimination between lesioned and nonlesioned hemispheres was not possible, the right and left hemispheres were arbitrarily assumed to be damaged and nondamaged, respectively. Thus, in these patients, ΔrCBFmean, ΔrCBFmax, and ΔrCBFmin were considered as the difference in rCBFmean, rCBFmax, and rCBFmin values between the right and left hemispheres.
Outcome Measurement

The neurological outcome at 1 year postinjury was measured by means of the Glasgow Outcome Scale (GOS) (27). For analytical purposes, 2 main categories were considered: favorable outcome, including good recovery and moderate disability, and unfavorable outcome, including severe disability, persistent vegetative state, and death.

Statistical Analysis

Three different levels of analysis were performed. On the first level, we investigated rCBF values in individual Xe-CT studies by comparing: 1) rCBF values between lesioned and nonlesioned hemispheres in each of the 3 patient groups (evacuated SDH, evacuated EDH, and diffuse injury) by means of a paired t test; and 2) rCBF and ΔrCBF values among the corresponding hemispheres of the different groups by means of analysis of variance, followed, if needed, by Sheffé’s post-hoc test.

In the second level of analysis, we calculated for each patient, the widest ΔrCBFmean, the widest ΔrCBFmax, and the widest ΔrCBFmin values, which summarized the widest value among all the corresponding ΔrCBFmean, ΔrCBFmax, and ΔrCBFmin values obtained from the Xe-CT studies. Subsequently, the differences between widest ΔrCBF values in outcome categories (favorable and unfavorable) were evaluated by means of a pooled t test.

Finally, we analyzed the time course of ΔrCBFmean, ΔrCBFmax, and ΔrCBFmin values calculated from multiple Xe-CT studies, obtained from each of the following groups: 1) patients with an evacuated SDH with an unfavorable outcome; 2) patients with an evacuated SDH with a favorable outcome; and 3) control patients with EDH or diffuse injury. These values were obtained for the 4 different time intervals (<24 hours, 24–96 hours, 4–7 days, and >7 days postinjury). ΔrCBFmean, ΔrCBFmax and ΔrCBFmin values were compared: 1) within each of the 3 groups by means of analysis of variance and post-hoc analysis (Sheffé test) when needed, and 2) among each of the 4 corresponding time frames of the 3 groups.

RESULTS

General Data

General characteristics of the 20 patients with isolated SDH and 23 control patients with EDH (11 patients) or diffuse lesions (12 patients) are reported in Table 1. In patients with SDH, the elapsed median time between trauma and surgery was 4.5 hours (interquartile range, 4.5 hours) and the mean decompression area was 82 cm² (standard deviation [SD], 18.5 cm²). The average thickness of SDH was 17.4 mm (SD, 11.9 mm).

Details of CBF Studies

Cumulatively, 81 Xe-CT studies in 43 patients were analyzed. The median time elapsing between injury and the Xe-CT studies was 98 hours (interquartile range, 128.5 hours). Forty-three Xe-CT studies were collected for the 20 patients with an evacuated SDH, 21 Xe-CT studies for the 11 patients with an evacuated EDH, and 17 Xe-CT studies for the 12 patients with diffuse injury.

Multiple Xe-CT studies were performed in 14 patients with SDH (2 Xe-CT studies in 10 patients, 3 Xe-CT studies in 2 patients, and >3 Xe-CT studies in 2 patients), in 8 patients with EDH (2 Xe-CT studies in 6 patients, 3 Xe-CT studies in 2 patients), and in 5 patients with diffuse injury (2 Xe-CT studies in 5 patients). During the Xe-CT studies, the mean physiological values were: ICP, 19.0 mm Hg (SD, 8.0 mm Hg); CPP, 71.3 mm Hg (SD, 12 mm Hg); PaCO₂, 38.7 mm Hg (SD, 6.1 mm Hg), and hematocrit (Ht), 29.6% (SD, 5.1%).

No differences were found among Xe-CT studies in patients with evacuated SDH, evacuated EDH, and diffuse injury for ICP (P = 0.7248), PaCO₂ (P = 0.3538), and Ht (P = 0.2662) values. Probably as the result of the intensive care unit treatment protocols, CPP values during the Xe-CT studies in the patients with evacuated SDH, evacuated EDH, and diffuse injury were not statistically different (P = 0.4787). Comparable CPP values were, however, obtained at the cost of different catecholamine regimens. In fact, the CPP levels were maintained more fre-
TABLE 1. Demographic and clinical characteristics of patients with evacuated acute subdural hematoma, evacuated extradural hematoma, and diffuse injury

<table>
<thead>
<tr>
<th></th>
<th>SDH (n = 20)</th>
<th>EDH (n = 11)</th>
<th>Diffuse injury (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>43.5 (17.6)</td>
<td>34.1 (16.3)</td>
<td>23.5 (11.8)</td>
</tr>
<tr>
<td>Male sex, no. (%)</td>
<td>16 (80%)</td>
<td>9 (81.8%)</td>
<td>10 (83.3%)</td>
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<td>ISS, median (IQR)</td>
<td>27 (6.5)</td>
<td>25 (1)</td>
<td>29 (16.5)</td>
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<td>AIS, median (IQR)</td>
<td>4.5 (1)</td>
<td>5 (0)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Hypotension, no. (%)</td>
<td>6 (30%)</td>
<td>4 (36.4%)</td>
<td>5 (41.2%)</td>
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<tr>
<td>Hypoxia, no. (%)</td>
<td>13 (65%)</td>
<td>7 (63.6%)</td>
<td>9 (75%)</td>
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<td>Motor GCS, median (IQR)</td>
<td></td>
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<td></td>
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<tr>
<td>Pre-hospital</td>
<td>4 (3.25)</td>
<td>5 (5)</td>
<td>5 (2.75)</td>
</tr>
<tr>
<td>At first hospital admission</td>
<td>2.5 (4)</td>
<td>2.5 (2.5)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>At NSH admission</td>
<td>3 (4)</td>
<td>2 (2.75)</td>
<td>2.5 (4)</td>
</tr>
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<td>Pupil reactivity to light at NSH admission, no. (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bilaterally reactive</td>
<td>9 (45.0%)</td>
<td>7 (63.6%)</td>
<td>11 (91.7%)</td>
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<tr>
<td>1 pupil dilated, unreactive</td>
<td>8 (40.0%)</td>
<td>4 (36.4%)</td>
<td>1 (8.33%)</td>
</tr>
<tr>
<td>Bilaterally unreactive</td>
<td>3 (15%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
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<td>Midline shift (mm) at worst CT, mean (SD)</td>
<td>14 (6.6)</td>
<td>9.3 (7.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mass volume (mL) at worst CT, mean (SD)</td>
<td>60.7 (41.3)</td>
<td>79.3 (58.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Compression of basal cisterns at worst CT, no. (%)</td>
<td>18 (90%)</td>
<td>8 (72.7%)</td>
<td>3 (25.0%)</td>
</tr>
<tr>
<td>ICP (mm Hg) during total LOS, mean (SD)</td>
<td>15.5 (3.8)</td>
<td>18.1 (3.7)</td>
<td>15.2 (5.5)</td>
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<td>CPP (mm Hg) during total LOS, mean (SD)</td>
<td>71.0 (5.7)</td>
<td>65.7 (6.2)</td>
<td>73.4 (7.9)</td>
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<td>TIL, no. (%)</td>
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<tr>
<td>Standard</td>
<td>1 (5%)</td>
<td>2 (18.2%)</td>
<td>2 (16.6%)</td>
</tr>
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<td>Reinforced</td>
<td>12 (60%)</td>
<td>8 (72.7%)</td>
<td>8 (66.7%)</td>
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<td>Extreme</td>
<td>7 (35%)</td>
<td>1 (9.1%)</td>
<td>2 (16.7%)</td>
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<td>Vasopressors, no. (%)</td>
<td>20 (100%)</td>
<td>9 (81.8%)</td>
<td>9 (75%)</td>
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<td>GOS, no. (%)</td>
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<tr>
<td>Dead</td>
<td>6 (30%)</td>
<td>0 (0%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Persistent vegetative state</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Severe disability</td>
<td>2 (10%)</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>3 (15%)</td>
<td>2 (18.2%)</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>Good recovery</td>
<td>7 (35%)</td>
<td>8 (72.7%)</td>
<td>5 (41.7%)</td>
</tr>
</tbody>
</table>

*a SDH, subdural hematoma; EDH, extradural hematoma; SD, standard deviation; ISS, injury severity score (3); IQR, interquartile range; AIS, abbreviated injury severity score for the head (2); GCS, Glasgow Coma Scale; NSH, neurosurgical hospital; CT, computed tomography; NA, not applicable; ICP, intracranial pressure; LOS, length of stay; CPP, cerebral perfusion pressure; TIL, therapeutic intervention level; GOS, Glasgow Outcome Scale.

Analysis of CBF Studies

rCBFmean and rCBFmax values were significantly higher beneath the removed SDH than in the contralateral area in patients with an evacuated SDH, whereas they were similar between the damaged and nondamaged hemispheres in patients with an evacuated EDH and in patients with diffuse injury (Table 2). In addition, rCBFmean and rCBFmax values obtained in the lesioned hemisphere were higher in evacuated SDH than in evacuated EDH and diffuse injury. However, although these differences were statistically relevant for rCBFmax (P = 0.042), they did not reach a significant level for rCBFmean (P = 0.0798). No statistical differences were found for rCBFmean and rCBFmax values measured in the contralateral hemisphere among patients with evacuated SDH, evacuated EDH, and diffuse injury (P = 0.8682 and P = 0.9039, respectively). rCBFmin values did not differ between the injured and contralateral hemispheres in each group examined (Table 2), nor among the lesioned (P = 0.077) and contralateral (P = 0.6586) hemispheres of the 3 different groups evaluated. Accordingly, ΔrCBFmean and ΔrCBFmax values were significantly higher (P = 0.00130 and P = 0.0018, respectively) in patients with evacuated SDH than in those with evacuated EDH or diffuse injury (Table 2), whereas ΔrCBFmin values were equivalent in the various groups analyzed.

As illustrated in Table 3, the analysis of rCBFmean, rCBFmax, and rCBFmin values, categorized according to CBF thresholds, demonstrated that, in patients with an evacuated SDH, levels consistent with relative and absolute hyperemia were more frequent than those suggestive of severe or moderate ischemia and reduced flow in both damaged and nondamaged hemispheres. Interestingly, rCBFmax values indicative of relative and absolute hyperemia were more commonly found under the evacuated SDH (58.1%) than in the contralateral area (39.5%).

**CBF Summary Values and Patient Outcome**

The data describing the severity, the physiological variables, and the therapeutic intensity level of treatment in patients with an evacuated SDH with an unfavorable outcome and in those with a favorable outcome are reported in Table 4. In comparison to SDH patients with a favorable outcome, those with an unfavorable outcome were older, with a lower motor GCS score, a higher frequency of pupil abnormalities (all not statistically significant), a greater thickness of SDH (P = 0.0144), a greater associated midline shift (P = 0.0473) before evacuation of the mass, and a shorter time interval between injury and SDH evacuation (P = 0.0364). No differences were found between the 2 groups regarding CPP levels and the use of vasopressors. No correlation was found between the time interval between injury and SDH evacuation and the ΔrCBF values.

In patients with an evacuated SDH, the widest ΔrCBFmax value was higher (P = 0.047) in 10 patients with an evacuated SDH and an unfavorable outcome (33.8 mL/100 g/min; SD,
In 10 patients with an evacuated SDH and a favorable outcome (13.1 mL/100 g/min; SD, 22.1 mL/100 g/min). In contrast, in 23 controls with an evacuated EDH or diffuse injury, there were no differences for the widest ΔrCBFmax value between patients with unfavorable (3 patients, −2.9 mL/100 g/min; SD, 4.7 mL/100 g/min) and favorable (20 patients, −3.8 mL/100 g/min; SD, 13.5 mL/100 g/min) outcomes (P = 0.90).
As reported in Figure 2, the widest ΔrCBFmax values were stratified in evacuated SDH patients and in controls according to 4 different GOS categories (good recovery, moderate disability, severe disability/persistent vegetative state, and death). An association between a gradual increase in the median of the widest ΔrCBFmax value and a progressive worsening in outcome category was observed only in patients with evacuated SDH. No differences were found for the widest ΔrCBFmean and ΔrCBFmin values between the 2 different GOS categories in patients with an evacuated SDH and in controls (data not shown).

| TABLE 4. Demographic and clinical characteristics of patients with evacuated acute subdural hematoma dichotomized according their final outcomea |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Unfavorable (n = 10) | Favorable (n = 10) | P value |
| Widest ΔrCBFmax (mL/100 g/min), mean (SD) | 33.8 (21.5) | 13.1 (22.1) | 0.047 |
| Age (y), mean (SD) | 49.4 (17.8) | 37.5 (16.5) | 0.091 |
| Male sex, no. (%) | 9 (90%) | 7 (70%) | 0.2636 |
| Direct admission to NSH, no. (%) | 4 (40%) | 5 (50%) | 0.6531 |
| Time interval between injury and SDH evacuation, median (IQR) | 4 (2) | 7.5 (48) | 0.0364 |
| Mean decompression area (cm²), mean (SD) | 80.5 (15.6) | 83.5 (21.8) | 0.7264 |
| ISS, median (IQR) | 27 (9) | 27 (12) | 0.8 |
| AIS, median (IQR) | 5 (1) | 4 (1) | 1 |
| Hypotension, no. (%) | 1 (10%) | 5 (10%) | 0.0510 |
| Hypoxia, no. (%) | 6 (60%) | 7 (70%) | 0.6392 |
| Motor GCS, median (IQR) | | | |
| Pre-hospital | 3 (1.5) | 5 (4) | 0.1416 |
| At NSH admission | 2.5 (3) | 3.5 (4) | 1.0 |
| Pupils reactivity to light at NSH admission, no. (%) | | | |
| Bilaterally reactive | 3 (30%) | 6 (60%) | 0.3998 |
| 1 pupil dilated, unreactive | 5 (50%) | 3 (30%) | |
| Bilaterally unreactive | 2 (20%) | 1 (10%) | |
| Thickness of SDH (mm) at CT, mean (SD) | 23.2 (13.4) | 11.5 (6.7) | 0.0144 |
| Midline shift (mm) at CT before SDH evacuation, mean (SD) | 16.9 (6.7) | 11.1 (5.4) | 0.0473 |
| Compression of basal cisterns before SDH evacuation, no. (%) | 9 (90%) | 9 (90%) | 1 |
| ICP (mm Hg) during total LOS, mean (SD) | 16.0 (4.3) | 15.1 (3.4) | 0.6103 |
| CPP (mm Hg) during total LOS, mean (SD) | 70.7 (4.8) | 71.3 (6.8) | 0.8349 |
| TIL, no. (%) | | | |
| Standard | 0 | 1 (10%) | 0.4780 |
| Reinforced | 7 (70%) | 5 (50%) | |
| Extreme | 3 (30%) | 4 (40%) | |
| Vasopressors, no. (%) | | | |
| Dead | 6 (60%) | NA | |
| Persistent vegetative state | 2 (20%) | NA | |
| Severe disability | 2 (20%) | NA | |
| Moderate disability | NA | 3 (30%) | |
| Good recovery | NA | 7 (70%) | |

a ΔrCBFmax, side-to-side difference in rCBFmax values; SD, standard deviation; NSH, neurosurgical hospital; SDH, subdural hematoma; IQR, interquartile range; ISS, injury severity score (3); AIS, abbreviated injury severity score for the head (2); GCS, Glasgow Coma Scale; CT, computed tomography; ICP, intracranial pressure; LOS, length of stay; CPP, cerebral perfusion pressure; TIL, therapeutic intervention level; GOS, Glasgow Outcome Scale; NA, not applicable.
Time Course Analysis of CBF Studies According to SDH Patient Outcome

No differences were found within ΔrCBFmean, ΔrCBFmax, and ΔrCBFmin values, obtained from 81 Xe-CT studies, and measured at the 4 time intervals for each of these 3 groups: 1) patients with an evacuated SDH and an unfavorable outcome (20 Xe-CT studies in 10 patients); 2) patients with an evacuated SDH and a favorable outcome (23 Xe-CT studies in 10 patients); and 3) controls (38 Xe-CT studies in 23 patients) (data not shown). Conversely, differences were found when ΔrCBF values measured in each time frame were compared among the same 3 groups. More specifically, ΔrCBFmean and ΔrCBFmax values were statistically different among the groups at 24 to 96 hours ($P = 0.0279$ and $P = 0.0023$, respectively) and at 4 to 7 days ($P = 0.0357$ and $P = 0.0040$, respectively). Post-hoc analysis showed that ΔrCBFmean and ΔrCBFmax values were significantly greater in patients with an evacuated SDH and an unfavorable outcome than in controls at 24 to 96 hours ($P = 0.0279$ and $P = 0.0073$, respectively) and at 4 to 7 days ($P = 0.0366$ and $P = 0.0279$, respectively). ΔrCBFmax values at 4 to 7 days were statistically higher ($P = 0.0144$) in patients with an evacuated SDH and an unfavorable outcome than in patients with an evacuated SDH and a favorable outcome.

The time course of ΔrCBFmax values in the 3 groups is shown in Figure 3, whereas in Figure 4, 2 illustrative cases describing the different time courses of rCBF levels in patients with an evacuated SDH and an unfavorable outcome (Fig. 4A), compared with patients with an evacuated SDH and a favorable outcome (Fig. 4B) are presented. No statistically significant differences were found in the 4 time intervals in each group of patients with an evacuated SDH, an evacuated EDH, and diffuse injury for CPP, ICP, PaCO₂, and Ht values. Similarly, no differences were found in the 4 time intervals in patients with an evacuated SDH and an unfavorable outcome compared with those with a favorable outcome for the same variables.

No statistically significant differences were found among the corresponding 4 time intervals in each group of patients with an evacuated SDH, an evacuated EDH, and diffuse injury for CPP, ICP, PaCO₂, and Ht values. Likewise, for the same variables, no differences were found in the corresponding 4 time intervals in patients with an evacuated SDH and an unfavorable outcome compared with patients with a favorable outcome. No statistical discrepancies were detected when the timing of ΔrCBFmin values was evaluated within each group and among corresponding time intervals for the different groups (data not shown).

**DISCUSSION**

The cortex underlying an evacuated acute SDH was predominantly associated with high rCBF values, which were frequently consistent with absolute hyperemia. This condition seemed to prevail in patients with an evacuated SDH and an unfavorable outcome, in whom rCBF levels progressively increased after the first 24 hours, reached their peak by the seventh day postinjury, and returned to initial values after 1 week. In the same patients with an unfavorable outcome, the presence of a greater thickness and of a greater midline shift before SDH removal suggests that the mass effect attributable to the SDH or its associated hemispheric swelling was more
with the most severe brain lesions or those who are unstable because of multiple extracranial injuries. Furthermore, cases with SDH associated with satellite contusions or hypodensity in the cortex beneath the lesion on CT scans before the surgical evacuation were excluded by the case mix selection. This selection bias could be consistent in the exclusion of patients at higher risk of focal and global ischemia and should be considered in the interpretation of the present results.

prominent. The level of hyperemia and the outcome of the patients did not seem to be associated with different levels of CPP and the use of vasopressors, suggesting that prolonged hyperemia was not the result of specific management but, rather, with the initial severity of the patients’ condition.

Selection Bias in Patients with Xe-CT Studies

As described in one of our previous studies (9), patients who undergo functional imaging usually do not include patients with the most severe brain lesions or those who are unstable because of multiple extracranial injuries. Furthermore, cases with SDH associated with satellite contusions or hypodensity in the cortex beneath the lesion on CT scans before the surgical evacuation were excluded by the case mix selection. This selection bias could be consistent in the exclusion of patients at higher risk of focal and global ischemia and should be considered in the interpretation of the present results.
The Cortex Underlying an Evacuated Acute SDH Can Be Hyperemic

The main result of the study was that, in brain tissue located beneath an evacuated SDH, elevated rCBF values suggestive of "absolute hyperemia" (44) predominated, whereas low rCBF levels indicative of "ischemia" (28) were lacking. Although a recent study by Cunningham et al. (13) has clearly demonstrated that the isolated measurement of CBF may predict brain ischemia only in a probabilistic perspective, elevated rCBF levels are less likely associated with ischemia than low rCBF values, even though PET studies (10) have shown that high rCBF levels can sometimes be inappropriate for metabolic demand.

Global (37, 40, 54) and regional (1, 8) elevation of rCBF is common in the time window of 24 to 96 hours. However, the prolonged hyperemic reaction in patients with an evacuated SDH beyond the first 96 hours seems to be a new finding, even if, in part, it has already been shown by Yamakami and Yamaura (64), who qualitatively measured CBF values by means of single photon emission computed tomography in a case series with TBI patients who were predominantly affected by SDH, all with external decompression. The reasons for the specific biological reactions involving the cortex beneath the SDH may be manifold and can be discussed here only speculatively, as CBF was the only physiological variable investigated by the study. Among these possible reasons, the occurrence of an early ischemic insult in this area before SDH evacuation may play an important role, as demonstrated by the high frequency of ischemia found in neuropahtological examinations of patients who died (19). Cerebral ischemia has been reproduced in the classic SDH animal model (42) in which a core of densely reduced rCBF has been detected beneath the SDH. This core usually enlarges after the removal of SDH, although in some animals, hyperemic values were found with a patchy distribution (32). In this study by Kuroda and Bullock (32), similar to findings in the present SDH patient series, the bone flap of the craniotomy was not repositioned while CBF was measured 1 hour after removal of the hematoma.

In humans, a reduction in regional and global CBF levels before evacuation, followed by their recovery after hematoma removal, was reported in 2 SDH patients by Schröder et al. (50). A decrease in rCBF values before SDH evacuation was confirmed, in association with severe intracranial hypertension and low CPP values, in another small case series (59), using laser Doppler flowmetry. Similarly, Gopinath et al. (18) demonstrated the appearance of deep jugular bulb desaturation before hematoma evacuation, suggesting the presence of a mismatch between perfusion and O₂ consumption. Therefore, with confirmation of the relevance of ischemia before the SDH evacuation, it is possible that, in cases not evolving to a severe, irreversible grade, after hematoma evacuation, the cortex that has previously been compromised because of compression of the microvessels (16) could be affected by postischemic luxury perfusion. This is believed to be a consequence of focal impaired autoregulation (35) and has been studied mostly in models of temporary macrovascular occlusion or in humans affected by stroke (36, 49). In trauma, focal macrovascular ischemia, usually attributable to vascular distortion, predominantly in the posterior cerebral artery territories, is less frequent and, as in stroke, may be followed by a partial reperfusion, as described by Furuya et al. (17). However, it is unclear whether this physiology is also applicable in trauma, in which ischemia is much more frequently microvascular (41) or attributable to reduced CPP.

Further extrapolations from stroke or middle cerebral artery occlusion models should be applied with caution to the results of the present study. Consequently, additional reasons may explain why a persistent vasodilation was observed over several days. The mass effect and the hemispheric compression attributable to SDH may be not the only factors promoting damage to the underlying brain. Accordingly, a marked increase in regional glucose consumption indicative of hyperglycolysis, attributed to a postischemic excitotoxic mechanism (6), was found by Kuroda et al. (33) in the area surrounding the densely ischemic core beneath the SDH, and it seems to be associated with uncoupled reduced rCBF values (31). Hyperglycolysis seems to be in part independent of the mass effect. In fact, it has been postulated that clotted subdural blood in contact with a large area of cortex can directly affect rCBF and activate hyperglycolysis (6). This highlights the findings on SDH produced in the Miller model (42), in which only moderate intracranial hypertension is produced and the ischemic damage appears to be mainly attributable to the local effects of blood overlying the cortex.

Recently, in the new model proposed by Sawauchi et al. (48), even diffuse brain injury and hypoxemia were included, with the attempt to more accurately reproduce the clinical scenario and to generate severe, sustained intracranial hypertension (48) and hemispheric swelling after evacuation (47). The authors speculated that, in such a setting, regional brain swelling was attributable to postischemic reperfusion, although physiological studies on rCBF in the cortex beneath the SDH have been not yet done.

In models of progressive intracranial hypertension such as intracranial balloon inflation (34) or fluid infusion into the cisterna magna (20), a compensatory vasodilation aimed at maintaining CBF despite a reduced CPP was observed in the majority of the brain tissue; however, in the area close to the balloon, the blood vessels were shown to be collapsed as a result of tissue pressure leading to regional ischemia (23, 61). In cases of extreme intracranial hypertension (with loss of autoregulation), the return to normal ICP was followed by prolonged vasodilation and reactive hyperemia. In contrast, in cases of moderate intracranial hypertension and preserved autoregulation, the return to normal ICP was associated with re-normalization of the caliber of cortical arteries, as shown when using a translucent window in the skull (62, 63).

Although most experimental studies observe the natural history of SDH for short periods, in humans the observation can be potentially more prolonged, but selective studies on SDH patients are lacking. Long-term observations are available only in isolated human studies. Bergsneider et al. (4) reported regional hyperglycolysis in 5 patients with TBI, 4 of them having an SDH, who were evaluated by means of PET studies performed after a median of 5 days postinjury. In the unique
patient with an evacuated SDH in whom it was possible to measure rCBF by means of Xe-CT on the same day as the PET study (the fifth day postinjury), the focal hyperglycolysis (an increase in the regional cerebral metabolic rate [CMR] of glucose) in the cortex beneath the evacuated SDH was associated with a corresponding increase of rCBF on Xe-CT.

Although studies on regional CMR of O2 are not available, patients with SDH underwent a reduction in global CMR of O2, which was demonstrated to be more pronounced, in another series by Valadka et al. (58), in patients with greater midline shift. These findings, suggesting a reduction of CMR of O2 and an increase in regional CMR of glucose, highlight the hypothesis that prolonged changes in rCBF levels detected in the cortex located beneath an evacuated SDH could be driven by a metabolic coupling with increased regional glucose metabolism. Furthermore, several other biological phenomena (14, 15) are involved in secondary damage and repair of the injured brain, including spreading depolarization, postischemic inflammation, which may be associated with hyperglycolysis (4), and apoptosis. Interestingly, the time course of these events (15) seems to correspond to the temporal pattern of hyperemia found in the affected side of our patients with an evacuated SDH and an unfavorable outcome.

Hyperemia in the Cortex Underlying an Evacuated Acute SDH Can Be Associated with Unfavorable Outcome

In traumatic brain injury, the development of global cerebral hyperemia is not a frequent occurrence and is often associated with elevated ICP and an unfavorable outcome (30). More controversial is the relevance of focal hyperemia, which was previously suggested to have a beneficial role in brain tissue surrounding traumatic contusions (45). In contrast, the part of our study focusing on the relationship existing between outcome and rCBF levels documented that hyperemic values predominated in the cortex located in the damaged hemisphere of patients with an evacuated acute SDH and an unfavorable outcome. In addition, only patients with an evacuated acute SDH and unfavorable outcome had a persistent hyperemic response in the same region. Moreover, in patients with an evacuated SDH, a progressive increase in rCBF levels in the cortex beneath the evacuated hematoma was associated with a corresponding worsening in the GOS category. The comparative analysis of initial severity of SDH patients suggests that patients with an unfavorable outcome had the most severe SDH. Interestingly, patients with an unfavorable outcome had a greater SDH thickness and midline shift before the evacuation. This latter variable, which was previously found by Valadka and Robertson (57) to be associated with a metabolic derangement of O2 consumption, might be considered a potential indicator of the extent of pre-evacuation compression, hemispheric swelling, and, possibly, ischemia of the cortex underlying the SDH. All these findings suggest that, in patients with an evacuated acute SDH, there could be a physiological link between focal hyperemia occurring in the brain tissue underlying an evacuated acute SDH and unfavorable outcome, probably consistent with the severity of initial brain damage and, particularly, the extent and the length of cortical compression before the SDH evacuation.

Overall, the relation of focal hyperemia to final outcome may be explained in 2 ways, which probably are not mutually exclusive: 1) focal hyperemia may be the result of an initial ischemic insult, thus representing a kind of “memory” of ischemia, leading to loss of regional autoregulation; or 2) focal hyperemia could reflect an adaptive-reparative response of injured cortex that is greater in patients who incurred more severe injury. The first explanation could be more appropriate in the first hours and days post-SDH evacuation, and the second could better explain the more delayed hyperemia.

It remains unclear, however, whether hyperemia could, perse, be a cause of further brain damage. Studies of macrovascular ischemia (22) suggest that prolonged hyperemia is not a direct cause of damage, but it is more probably associated with postischemic swelling and poor tissue outcome, being a collateral aspect of initial ischemia. Nevertheless, as a part of the same biological process, a more intense prolonged hyperemia may worsen the reperfusion injury (49). Conversely, in macrovascular ischemia models, early postischemic reperfusion is frequently associated with a recovery of tissue and a favorable outcome (36), probably because it reflects the short duration of macrovascular occlusion.

Limitations of the Study

The limitations related to the snapshot nature of the Xe-CT technique and those associated with the potential overestimation of CBF promoted by Xe-induced flow activation have been described in our previous studies (7–9). A methodological limitation of the study was that we did not investigate the fate of the tissue beneath the removed SDH in the follow-up CT scans by the evaluation of atrophy severity. This precluded the possibility to definitively relate tissue outcome to the intensity and the duration of hyperemia and, finally, to neurological outcome.

Furthermore, in this study, the multiple variables affecting global and regional cerebral perfusion could not be completely investigated or standardized. In fact, it is now established that, because patients with acute SDH may have severe intracranial hypertension before evacuation, the timing of surgery is highly relevant to reducing brain tissue injury (51). In addition, experimental studies (47, 48) suggest that diffuse brain injury and hypoxia can greatly contribute to the secondary damage of brain parenchyma in the presence of an acute SDH. However, none of these factors can be controlled as in a laboratory setting, and this may explain the variability in our data.

A further shortcoming of the current study is that our findings are not able to give any definitive explanation regarding the predominant causes of rCBF elevation found in the cortex located beneath an evacuated acute SDH which are not supported either by results obtained by local biochemical (microdialysis) (24), oxygenation (partial pressure of tissue O2) (24), or regional O2 extraction and glucose metabolism (PET) (4, 10), nor by data coming from functional imaging (magnetic resonance imaging diffusion studies) (38). Furthermore, although the study was based on CBF measurements, it cannot improve
the understanding of the cellular and molecular components and causes of traumatic cerebral vascular injury (14).

Finally, in the present series, all patients were left without bone flap reposition after the SDH evacuation, according to widespread neurosurgical practice (11), and the influence of this surgical approach on rCBF levels should be considered in the analysis and interpretation of the data. In fact, an experimental study suggested an association between an increase in rCBF values and regional swelling (12), and clinical studies showed an increase in rCBF (64) and velocimetry at the level of the decompressed hemisphere (5). An illustrative case recently reported by Valadka and Robertson (57) showed that, after external decompression, hyperemia occurs independently, regardless of the presence of an evacuated acute SDH on initial CT. However, all the results obtained in these investigations are difficult to evaluate, owing to the lack of a control group in such studies. External decompression has no effect on normal brain perfusion (21), and regional hyperemia might be the result of the natural history of the evacuated SDH, independent of the external decompression. The latter could be a factor merely facilitating regional hyperemia by means of a decrease in regional intracranial hypertension on the cortex beneath the bone flap. Considering our results, patients with an unfavorable outcome and regional hyperemia were associated with a greater midline shift before SDH evacuation but did not undergo a more extensive area of decompression, a finding which could reduce the chances that external decompression directly affects hyperemia. Furthermore, it is important to note that, in our study, external decompression, once considered a potential independent risk factor for hyperemia, was uniformly distributed in all of the SDH patients.

**Clinical Implications of the Study**

Cerebral hyperemia is sometimes considered a potential cause of increased blood volume and intracranial hypertension, when intracranial compliance is exhausted (30). Consequently, practical clinicians, when dealing with hyperemia measured after perfusion studies, might be tempted to use cerebral vasoconstrictors, to reduce vasodilation, or to maintain CPP values at the lower level of the autoregulatory range. This potential approach could be based on the concept that hyperemia outweighs the metabolic demands of tissue, but this can be untrue in brain affected by injury and actively involved in reparative activity (10, 26). However, such an approach should be supported by multiparametric measurements, including the combined evaluation of both perfusion and metabolic variables. In fact, the interpretation of rCBF abnormalities such as hyperemia or ischemia should be considered according to metabolic requirements (10, 25).

Traumatic cerebral vascular injury reduces or abolishes a variety of compensatory vasodilatory and vasoconstrictory responses related to changes in arterial blood pressure, blood gas levels, and blood viscosity as well as cerebral metabolic activity (14). The focal hyperemia found in the cortex underlying the evacuated SDH is probably associated with a more severe derangement of regional autoregulation, making the tissue more sensitive to secondary insults. Consequently, regional hyperemia detection should alert clinicians to consider the affected cerebral region as being at risk of further damage, instead of considering it protected by the apparently overabundant rCBF levels.

**CONCLUSION**

This study shows that, after the evacuation of an acute SDH, the cortex located beneath the removed lesion may be affected by long-lasting hyperemia. The causes of this perfusion response need to be investigated, but the relationship between hyperemia, greater SDH thickness, and midline shift before SDH removal and unfavorable neurological outcome suggests that the elevation of rCBF levels in brain tissue underlying an evacuated acute SDH could be dependent on a more severe degree of initial damage.

**Disclosure**

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

Chiaregato et al. describe their analysis of the relationships between cerebral blood flow (CBF) as measured by Xe-computed tomographic (CT) studies, the presence of evacuated acute subdural hematoma (SDH), and neurological outcome in 20 patients with moderate or severe traumatic brain injury (TBI). The comparison group consisted of 23 patients with moderate or severe TBI with diffuse injury or an evacuated epidural hematoma. The differences in maximum and mean CBF between the 2 sides were greater in SDH patients than in controls. Differences in maximum CBF between the sides were generally greater in SDH patients with unfavorable as opposed to favorable outcomes, and they were also greater in SDH patients with an unfavorable outcome than in controls. Unfavorable outcome was associated with greater thickness of SDH and with a greater degree of midline shift. The authors conclude that elevation of regional CBF values occurs frequently in the cerebral cortex underlying an evacuated SDH. This elevated CBF seems to be associated with unfavorable outcome and may persist for several days. Of note, the bone flaps were not replaced in the patients who underwent evacuation of their SDH, and the effect of decompressive craniectomy on subsequent measurements of CBF remains unclear. Nevertheless, this study is a valuable contribution to our understanding of the complex interplay among TBI, SDH, and CBF.

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This is an interesting observational study of hemispheric hyperemia, demonstrated by Xe-CT studies after evacuation of acute SDH, and its association with unfavorable outcomes. It is postulated that this occurs as a result of postischemic luxury perfusion in association with focally impaired autoregulation. The authors question whether such hyperemia contributes to further secondary injury and, thus, produces worse outcomes. In my opinion, it is more likely that this finding is a reflection of the degree and extent of the primary underlying brain injury. Regardless, the clinical utility of this finding is debatable as it appears to have been unaffected by currently available therapies, including decompressive craniectomy.

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Chiaregato et al. measured CBF in the first week after surgical evacuation of an acute SDH in 20 patients with moderate and severe head injury. Patients included in this study were those without radiographic evidence of underlying “satellite contusions” or “areas of hypo-attenuation” and stable enough to undergo Xe-CT scanning. The authors found higher blood flows in the hemisphere with the original SDH than in the contralateral hemisphere, and CBF levels were sustained for up to the 7 days of the study period, whereas the differences were more pronounced in patients with larger midline shift or with poorer outcome (at 1 year). Such interhemispheric differences were not found in patients with diffuse injury (n = 12) or with an evacuated epidural hematoma (n = 11).

These findings are somewhat at odds with earlier reports, as cited by the authors. The difference between those earlier series and the present one is that all patients here not only had their SDH removed but also underwent a decompressive craniectomy, something rarely, or not at all, the case in other series. Considering this decompressive craniectomy, the data are in agreement with those of Yamakami and Yamaura (2), who found that hyperemia after this maneuver lasts 1 week, while flow values gradually diminish to expected values by 1 month.

At this point, one can only speculate about the cause for this increased CBF. One explanation would be that the hemisphere under the craniectomy swells more, not only because of an increase in cellular and interstitial edema, but also because of increased cerebral blood volume (CBV). Considering the formula: CBF = CBV × MTT, where MTT is mean transit time, one can imagine that, in the injured hemisphere, regulation of CBF is lost, and therefore an increase in CBV is not offset by a proportionate decrease in MTT, resulting in increased CBF. This could be investigated further by measuring CBV or MTT (the authors could probably do that themselves, retrospectively, as the Xe-CT CBF method is based on these measurements), or by measuring tissue oxygen content.

The clinical significance of these findings is not clear, but they would make one a little less fearful of causing ischemia with hyperventilation or with not raising the blood pressure to the “magic threshold” of cerebral perfusion pressure at 60 to 70 mm Hg. However, rather than using blood flow measurements, this is better monitored with measurements of oxygen availability or extraction.

Finally, one should keep in mind that this “elevated” CBF turns to hyperperfusion at approximately 1 month after the decompression, correlates with clinical findings, and can be reversed by reimplantation of the bone flap (1).

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This is an important article. It presents a large series of selected “pure” acute SDH patients, all with Xe-CT measurement of CBF in a total of 81 studies in 43 patients. Patients with associated contusions and “infarcts” on the postoperative CT scan were excluded. This is likely the largest such series of CBF studies in acute SDH. It is important because it supports the utility of the use of Xe-CT scanning at a time when it is very difficult to use this method, in the United States, because of Food and Drug Administration issues. The study shows that Xe-CT examination of CBF is an important prognostic indicator, and that, the higher the post-removal CBF (i.e., the more marked the postischemic hyperemia), the worse the patients did. Also, the larger the SDH, the more delay to evacuation, and the greater the shift, the higher the CBF, and the worse the outcome. Again, this corroborates the severity of the postischemic reperfusion phenomenon. This hyperemia persisted as long as 4 to 7 days, much longer than in stroke, and longer than is seen in any animal models. This posttraumatic hyperemia may be a cause of high intracranial pressure, which is almost always a huge management problem after acute SDH. The mechanism of the prolonged post-removal hyperemia shown in this study is unknown, yet the literature has much on the topic, with regard to stroke especially, and mechanisms such as acidosis, cytokine release, free radical activation, hyperglycolysis, and vasoparalysis, as well as the role of other vasodilators liberated from the clot, have all been proposed. Microdialysis studies have shown that glutamate and lactate are elevated 10- to 20-fold above normal in this tissue under the acute SDH, but cytokines have been little studied. The small numbers of studies done with acute SDH in situ (e.g., in animal models) and in humans confirm how severe the reduced CBF is, when acute SDH is present (3–7 mL/100 g/min), which is somewhat lower than the “trickle perfusion” that is seen after human occlusive stroke (10–14 mL/100 g/min).

Finally, these data strongly suggest that bad outcomes follow prolonged hyperemia. It would be most useful to assess tissue atrophy in the hemisphere on follow-up scans and to relate this to the duration and intensity of hyperemia.

Robertson’s group recently found that post-infarction brain reperfuses partially after TBI (e.g., after herniation syndromes with occlusion of the posterior cerebral artery), but contused brain, in contrast, reperfuses very poorly. This article makes another important contribution, namely the role of hyperemia in seemingly “normal-looking brain” under an acute SDH, after removal. It would be interesting if the authors would now focus on the other important group of acute SDH patients with rapidly developing low density on CT, under the clot. These patients are usually characterized by subpial hemorrhage, seen at surgery, and worse outcome. Our studies in the rat suggested profound long-term ischemia, even after removal of the clot, in such circumstances, but, so far as I am aware, this has not yet been validated in humans.

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