Hemostatic Activation in Spontaneous Intracerebral Hemorrhage

Yukihiko Fujii, MD, PhD; Shigekazu Takeuchi, MD, PhD; Atsuko Harada, MD; Hiroshi Abe, MD, PhD; Osamu Sasaki, MD, PhD; Ryuichi Tanaka, MD, PhD

Background and Purpose—There is no in-depth information available on the changes in hemostatic systems in patients in the acute phase of spontaneous intracerebral hemorrhage (ICH). This study was conducted to assess the relationships between the changes in hemostatic systems and clinical parameters in patients in acute-phase ICH.

Methods—The records of 358 patients admitted within 6 hours of onset of ICH were reviewed to examine the relationships between changes in hemostatic systems and computed tomographic findings and clinical parameters.

Results—The white blood cell counts and the levels of thrombin-antithrombin complex, plasmin-antiplasmin complex, and D-dimer in patients with intraventricular extension (IVE) or subarachnoid hemorrhage (SAH) were significantly (P<0.05) higher than those in patients without IVE or SAH. Most of the hemostatic system parameters in patients without IVE or SAH showed no significant differences compared with normal subjects. Multiple linear regression analysis revealed that the levels of thrombin-antithrombin complex significantly increased with an increase in the amount of SAH (P<0.001) and IVE (P<0.001). The levels of thrombin-antithrombin complex were not significantly associated with the volume of intraparenchymal hematoma. The level of the complex, however, was significantly (P<0.001) and independently associated with the presence of IVE or SAH (multiple logistic regression analysis).

Conclusions—The systemic activation of hemostatic systems in ICH patients seems to take place only when blood reaches the subarachnoid space. The intraparenchymal hematoma itself seems unlikely to activate hemostatic systems in peripheral blood, although the hematoma is expected to cause local activation of hemostatic systems. (Stroke. 2001;32:883-890.)

Key Words: blood coagulation ■ cerebral ventricles ■ hemostasis ■ intracerebral hemorrhage ■ subarachnoid hemorrhage

Stroke patients are at high risk for coagulopathies, such as disseminated intravascular coagulation and deep vein thrombosis. These patients, especially subarachnoid hemorrhage (SAH) patients, also show a high likelihood for the physiological activation of hemostatic systems in the ultraacute stage of stroke, although the mechanism for this activation remains unclear. On the other hand, to the best of our knowledge, no study has reported in detail a relationship between hemostatic activation and spontaneous intracerebral hemorrhage (ICH) in a large series of ICH patients, although a number of reports indicated impaired hemostasis as a risk factor for ICH. It is necessary to understand the physiological activation of hemostatic systems in ICH patients in both diagnosing coagulopathies and assessing the mechanism of hemostatic activation for stroke patients. These circumstances prompted this study.

The purpose of this study was to assess systemic hemostatic activation in patients in the acute phase of ICH. For this purpose, we reviewed the records of patients admitted within 6 hours of onset and examined relationships between the computed tomographic (CT) findings of ICH and hemostatic parameters, including sensitive markers, to detect the activation of hemostatic systems, such as thrombin-antithrombin complex.

Subjects and Methods

Patient Population

This study was performed according to the human research guidelines of the Internal Review Board of University of Niigata. Informed consent for this study was obtained from all participants (patients or their families). Between January 1990 and December 1996, 779 patients having nontraumatic intracerebral hematoma on the initial CT were admitted to our hospital. Of these, ICH was diagnosed in 559 patients, excluding 220 patients (196 with a secondary intracerebral hematoma and 24 receiving anticoagulation or antiplatelet therapy), as shown in Figure 1. Of the 559 patients, 201 who were admitted after 6 hours of onset or whose appearance of symptoms was uncertain were excluded. Thus, 358 patients (212 men and 146 women) were admitted to our hospital within 6 hours of onset of ICH (Figure 1). The time of onset was determined from the appearance of symptoms. Only patients admitted within 6 hours of onset were studied for the following reasons: to assess the
hemostatic condition of patients in the acute stage of ICH and to minimize the possibility of involvement of patients with hemorrhagic transformation of cerebral infarction.

In addition to plain CT and contrast medium-enhanced CT, all patients underwent either magnetic resonance angiography or conventional cerebral angiography to exclude hemorrhages caused by definite intracranial disease, such as cerebral aneurysms. This series of patients did not include those having ischemic stroke underlying intracerebral hemorrhage. None of the 358 ICH patients presented a marked reduction in fibrinogen levels or platelet counts, which indicated that our series included no ICH caused by disseminated intravascular coagulation (DIC).

We reviewed the records of these 358 patients. The hematoma sites were as follows: the putamen in 159 (including 37 with large hematomas involving the thalamus), thalamus in 90, brain stem in 45, cerebellum in 34, subcortex in 26, and caudate head in 4 (Table 1).

For comparison, 106 age-matched healthy subjects having no liver dysfunction, no diagnosis of stroke or heart disease, and no history of antiplatelet or anticoagulate therapy were hematologically examined.

**CT Findings**

All patients underwent a CT scan within 30 minutes of arrival. CT scans were performed on 5-mm-thick slices in all patients, and the intraparenchymal hematoma volume (hematoma volume in mL) was determined with the use of an area calculation program built into the CT scanner. The severity of intraventricular extension (IVE) on initial CT was classified into the following 3 mutually exclusive groups: (1) none, no evidence of clots in the ventricles; (2) mild, massive hematoma in 1 ventricle (bilateral lateral ventricles, third ventricle, and fourth ventricle); and (3) severe, massive hematoma in ≥2 of the 4 ventricles. The severity of SAH on initial CT was graded into the following 3 mutually exclusive groups: (1) none, no evidence of clots in the subarachnoid space; (2) mild, thin clots in the subarachnoid space; and (3) severe, massive clots in the subarachnoid space. Readers were blinded from patients’ records.

**Data Collection**

Immediately after admission, the patients’ neurological findings were assessed, and their systemic blood pressures was measured. The time of onset and medical history, including alcohol intake, were ascertained from the patient or family. The amount of daily alcohol consumption was calculated with the following formula: the volume (cm³) of the drink multiplied by the alcohol concentration (g/cm³) of the drink. All stroke patients routinely had 20 mL of blood taken for laboratory studies within an hour of admission. Blood was carefully drawn for laboratory examination with a multiple-syringe technique to avoid any artificial activation of the hemostatic system. The first 1 mL of blood was used for a blood cell count with the S-PLUS JR (Couler), the next 4.5 mL was carefully placed into a plastic tube containing 0.5 mL of 3.1% citrated buffer and used to determine platelet aggregability within an hour of blood collection. The last 9 mL was transferred into a prechilled plastic tube containing 1 mL of 3.1% citrated buffer, and the plasma was used to determine pro-thrombin time, activated partial thromboplastin time, and fibrinogen level. The remaining plasma was stored frozen at −70°C until it was used for batch analyses of other hemostatic parameters. To evaluate the activation of hemostatic systems, the levels of thrombin-antithrombin complex (Enzygnost TAT, Behringwerke), plasmin-antiplasmin complex (a2 PI Complex, Teijin), and D-dimer (LPIA, Iatron) were determined through enzyme immunoassays. All assays were completed within 1 month of blood collection. To assess the platelet aggregability, we determined levels of enhancement of platelet sensitivity using the modified method reported by Fishman et al. Enhancement of platelet sensitivity was defined as the lowest concentration of ADP that produces complete second-wave aggregation.
The age of ICH patients with IVE or SAH (64.3 ± 11.8 years) was significantly higher than that of ICH patients without IVE or SAH (61.3 ± 11.8 years). The systolic blood pressure at admission in the patients with IVE or SAH (185 ± 34 mm Hg) was significantly higher than in those without IVE or SAH (177 ± 32 mm Hg). The hematoma volume in the patients with IVE or SAH (37 ± 40 mL) was significantly greater than that in those without IVE or SAH (16 ± 19 mL). Consciousness disturbance was observed in 195 of the 358 patients (54.5%). The incidence of consciousness disturbance (69.5%) in the patients with IVE or SAH was significantly greater than that (37.5%) in those without IVE or SAH. No significant difference was found in the distribution of sex and the amount of habitual alcohol intake between the patients with and without IVE or SAH. For the time interval from onset to arrival, no significant difference was seen between patients with and without IVE or SAH.

### Hematological Parameters

The mean values of white blood cell counts and the levels of thrombin-antithrombin complex, plasmin-antiplasmin complex, and D-dimer in ICH patients were significantly higher than in normal subjects (Table 2). There were no significant differences in the other parameters, including platelet counts and fibrinogen levels, between ICH patients and normal subjects.

The white blood cell count in the patients with IVE or SAH was significantly higher than in those without IVE or SAH (Table 2). The platelet count, level of hemoglobin, enhancement of platelet sensitivity, fibrinogen level, and prothrombin and activated partial thromboplastin times showed no significant difference between the patients with and without IVE or SAH. The levels of the thrombin-antithrombin complex (an indicator of the activation of blood coagulation system), plasmin-antiplasmin complex (an indicator of the activation of fibrinolytic system), and D-dimer (an indicator of the activation of blood coagulation and fibrinolytic systems) in the patients with IVE or SAH were significantly higher than in those without IVE or SAH. No significant difference was found in the hematological parameters examined, excluding the white blood cell count, between the patients without IVE or SAH and normal subjects. Figure 2 shows the distribution of the levels of thrombin-antithrombin complex, plasmin-antiplasmin complex, and D-dimer in individual patients with or without IVE or SAH.

### Results

#### CT Findings and Clinical Parameters

Table 1 shows relationships among ICH sites and the presence of IVE or SAH on the initial CT. Of the 358 patients, 190 (53.1%) had IVE or SAH; i.e., 179 patients had IVE, 60 had SAH, and 46 had both IVE and SAH. The severity of IVE was none in 179, mild in 113, and severe in 66 patients. The severity of SAH was none in 298, mild in 49, and severe in 66 patients. The hematoma volume in the patients with IVE or SAH (37 ± 40 mL) was significantly greater than that in those without IVE or SAH (16 ± 19 mL). Consciousness disturbance was observed in 195 of the 358 patients (54.5%). The incidence of consciousness disturbance (69.5%) in the patients with IVE or SAH was significantly greater than that (37.5%) in those without IVE or SAH. No significant difference was found in the distribution of sex and the amount of habitual alcohol intake between the patients with and without IVE or SAH. For the time interval from onset to arrival, no significant difference was seen between patients with and without IVE or SAH.
revealed that the level of thrombin-antithrombin complex and white blood cell count were significantly and independently \((P<0.001\) and \(P<0.005\), respectively) associated with the presence of IVE or SAH (Table 3). White blood cell counts and levels of thrombin-antithrombin complex, plasmin-antiplasmin complex, and D-dimer significantly increased with an increase in the amount of IVE. They also significantly increased with a greater degree of SAH (Table 4).

Multiple linear regression analysis was performed to determine independent factors associated with the activation of the blood coagulation system (Table 5). For this analysis, the level of thrombin-antithrombin complex was selected as a response variable because of the closest association between the complex levels and the presence of IVE or SAH (Table 3). In the 190 patients with IVE or SAH, the levels of thrombin-antithrombin complex significantly and independently rose with an increase in the amount of IVE (standard \(\beta\) coefficient, \(0.352; P<0.001\)) and SAH (\(\beta=0.309, P<0.001\)) and age \((\beta=0.141, P<0.05)\). In the 168 patients without IVE or SAH, the levels of thrombin-antithrombin complex were not significantly associated with the (intraparenchymal) hematoma volume. Multiple logistic regression analysis revealed that the

### TABLE 3. Multiple Logistic Regression Analysis of the Presence of IVE or SAH and the Levels of Hematological Parameters and the Hematoma Volume

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>t Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematological parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell, (\times 10^3/\text{mm}^3)</td>
<td>1.20</td>
<td>1.07–1.34</td>
<td>3.16</td>
<td>0.002</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>0.91</td>
<td>0.74–1.11</td>
<td>−0.95</td>
<td>0.341</td>
</tr>
<tr>
<td>Platelet, (\times 10^5/\text{mm}^3)</td>
<td>0.95</td>
<td>0.90–1.01</td>
<td>−1.77</td>
<td>0.583</td>
</tr>
<tr>
<td>Enhancement of platelet sensitivity, (\mu\text{mol})</td>
<td>0.96</td>
<td>0.84–1.10</td>
<td>−0.55</td>
<td>0.583</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>1.00</td>
<td>0.99–1.00</td>
<td>−0.46</td>
<td>0.647</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>1.16</td>
<td>0.82–1.62</td>
<td>0.84</td>
<td>0.405</td>
</tr>
<tr>
<td>Activated partial thromboplastin time, s</td>
<td>0.91</td>
<td>0.80–1.04</td>
<td>−1.36</td>
<td>0.174</td>
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<td>Thrombin-antithrombin complex, ng/mL*</td>
<td>1.10</td>
<td>1.04–1.17</td>
<td>3.40</td>
<td>&lt;0.001</td>
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<tr>
<td>Plasmin-antiplasmin complex, (\mu\text{g/mL})</td>
<td>1.35</td>
<td>0.89–2.05</td>
<td>1.40</td>
<td>0.164</td>
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<tr>
<td>D-dimer, (\mu\text{g/mL})</td>
<td>1.22</td>
<td>0.90–1.66</td>
<td>1.27</td>
<td>0.204</td>
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<tr>
<td><strong>Thrombin-antithrombin complex and hematoma volume</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombin-antithrombin complex, ng/mL*</td>
<td>1.16</td>
<td>1.11–1.22</td>
<td>6.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraparenchymal hematoma volume, mL</td>
<td>1.00</td>
<td>0.99–1.01</td>
<td>0.528</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*The level was significantly and independently associated with the presence of IVE or SAH (multiple logistic regression analysis).
levels of thrombin-antithrombin complex were significantly \((P<0.001)\) and independently associated with the presence of IVE or SAH, although the (intraparenchymal) hematoma volume was not significantly associated with the presence of IVE or SAH (Table 3). Figure 3, which demonstrates the relationship between the levels of thrombin-antithrombin complex and hematoma volume in individual patients with and without IVE or SAH, shows that the levels of thrombin-antithrombin complex in patients with IVE or SAH were higher than in those without IVE or SAH, regardless of hematoma volume.

### Discussion
The present study provides 2 important pieces of information. First, it indicates the hemostatic condition of patients in the acute stage of ICH. To date, there has been no detailed research regarding physiological changes in the hemostatic system associated with ICH. Second, this study provides us with clues to elucidate the mechanism of hemostatic activation in hemorrhagic strokes, including SAH.

The definition of hemorrhagic stroke in the present study did not include hemorrhagic transformation of cerebral infarction. Hemorrhagic transformation, a serious problem in the clinical care of patients with acute cerebral infarction, has been extensively studied from clinical and experimental standpoints.\(^{14-32}\) There is, however, a significant difference in the hemostatic condition between ICH and the hemorrhagic transformation. The hemorrhagic transformation hemostatic systems in patients in the setting of ischemic stroke are in a...
systemically and markedly activated state before its occurrence, which may be attributable to ischemic injury to a large area of brain tissue or residual thrombi in the heart. On the other hand, in ICH patients, those systems are not expected to be in a significantly activated state before onset. Thus, in this study, we tried to exclude patients with hemorrhagic transformation using strict exclusion criteria. We believe our series of ICH patients included none with hemorrhagic transformation, although it is not possible to completely exclude all of them. Hence, we will discuss the hemostatic condition in patients with ICH excluding hemorrhagic transformation of cerebral infarction.

Hemostatic Activation in Spontaneous Intracerebral Hemorrhage

The white blood cell count and levels of thrombin-antithrombin complex, plasmin-antiplasmin complex, and D-dimer in ICH patients with IVE or SAH were much more elevated than in those without IVE or SAH. In ICH patients showing neither IVE nor SAH, the mean levels of hematological parameters examined here, with the exception of the white blood cell count, were not significantly different from those in normal subjects. An increase in white blood cell count indicates various conditions, such as infection, trauma, and stress. However, an increase in the levels of thrombin-antithrombin complex, plasmin-antiplasmin complex, and D-dimer indicates the activation of the blood coagulation system, the fibrinolytic system, and both these systems, respectively. Thus, in ICH patients, IVE or SAH seemed much more responsible for the systemic activation of hemostatic systems than intracerebral (intraparenchymal) hematoma. The intraparenchymal hematoma itself does not seem to systemically activate hemostatic systems to a great degree, although it may activate the surrounding hemostatic systems in the brain. Hence, in patients having neither IVE nor SAH, an increase in the levels of thrombin-antithrombin complex, plasmin-antiplasmin complex, and D-dimer seems to indicate that they may have coagulopathy, such as DIC or deep venous thrombosis. On the other hand, in patients having either IVE or SAH, an increase in those hemostatic parameters possibly indicates a physiological reaction, i.e., their having no coagulopathy such as DIC. Hence, when coagulopathy is diagnosed in ICH patients, it should be noted that there is a significant difference in the activation of hemostatic systems between the patients with and without IVE or SAH.

A lack of the above-mentioned information results in misinterpretation of the activation of the hemostatic systems in ICH patients. In a study regarding the relationship between hemostatic systems and ICH, those authors reported that the thrombin-antithrombin complex values significantly increased with an increase in hematoma volume and that patients with an insufficient elevation of the thrombin-antithrombin complex values had a high risk of hematoma enlargement. However, they carried out a univariate analysis on a small number of patients without any consideration of the presence of IVE or SAH, with a resulting misinterpretation of the data and the presentation of misinformation to readers.

Mechanisms of Hemostatic Activation in Hemorrhagic Stroke

The mechanism responsible for hemostatic activation in patients with hemorrhagic stroke remains uncertain. In our previous study of SAH, we proposed the following mechanisms for hemostatic activation in patients with SAH: (1) systemic activation of hemostatic systems by rapidly increased intracranial pressure or severe meningeal stimulation through unknown neurogenic or humoral mechanisms; (2) systemic activation by entry of a dissolved clot into the systemic blood circulation with or without cerebrospinal flow; and (3) local activation by damaged brain tissue, including cortical vessels. In the present study, investigations into hemostatic changes in ICH patients provided us with clues to elucidate the mechanism of hemostatic activation in hemorrhagic strokes.

The (intraparenchymal) hematoma volume itself did not correlate with the level of thrombin-antithrombin complex, i.e., the activation severity of the blood coagulation system. Thus, increased intracranial pressure, as a result of an increase in the hematoma volume itself, does not appear to systemically activate hemostatic systems. Meningeal stimulation through unknown neurogenic or humoral mechanisms is unlikely to be responsible for such severe systemic activation of hemostatic systems, as we observed in this study.

In our previous study, we reported that the levels of thrombin-antithrombin complex dramatically dropped 3 days after onset, regardless of the volume of residual clot in the subarachnoid space. Thus, although dissolved clots enter the systemic blood circulation with or without cerebrospinal flow and promote coagulant activity, the clots are unlikely to activate the systemic hemostatic systems to such a great degree as observed in this study.
The levels of thrombin-antithrombin complex in patients with ICH were independently associated with the severity of IVX and SAH, although the levels of the complex had no significant association with hematoma volume. The clot in the ventricles can easily enter the subarachnoid space. These facts support the hypothesis that the entry of blood into the subarachnoid space is much more responsible for the systemic activation of hemostatic systems than the intraparenchymal hematoma. Although the intraparenchymal hematoma is expected to cause local activation of hemostatic systems to a limited degree, it seems unlikely to activate hemostatic systems in peripheral blood.

These findings provide us with clues to elucidate the mechanism of systemic activation of hemostatic systems in hemorrhagic strokes. However, it remains unclear how the entry of blood into the subarachnoid space systemically activates hemostatic systems. Acute severe brain trauma, which usually accompanies traumatic SAH and injury to superficial brain tissue, most frequently results in tissue factor release and the generation of transient DIC. Thus, the entry of blood into the subarachnoid space may cause a considerable amount of tissue factor to release into systemic circulation through injury to superficial brain tissues, including superficial cerebral arteries, resulting in systemic hemostatic activation.

Conclusions

The systemic activation of hemostatic systems in ICH patients seems to take place only when blood reaches the subarachnoid space. The intraparenchymal hematoma itself seems unlikely to activate hemostatic systems in peripheral blood, although the hematoma is expected to cause local activation of hemostatic systems to a limited degree.

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References


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