Fibrin Clot Properties in Acute Stroke
What Differs Cerebral Hemorrhage From Cerebral Ischemia?

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Background and Purpose—Fibrin clot formation is important in acute intracerebral hemorrhage (ICH). We investigated plasma fibrin clot characteristics in acute ICH compared with acute ischemic stroke (IS) and nonstroke conditions.

Methods—In the 3 studied groups, we analyzed plasma fibrin clot phenotype and its association with clinical stroke presentation.

Results—Compared with controls, in patients with acute strokes, fibrin clots presented with lower clot permeability, longer lysis time, and higher maximum clot absorbance (for all, \( P < 0.001 \)). In ICH patients compared with IS patients, only lysis time was shorter by 13\% (\( P < 0.001 \)). In the ICH group, neurological deficit correlated significantly (\( P < 0.05 \)) with clot compaction, and the rate of increase in D-dimers released from clots, whereas initial hematoma volume correlated with lag phase of fibrin formation on turbidimetry and compaction (\( P < 0.05 \)).

Conclusions—In both types of acute strokes, fibrin clot properties are altered: denser fibrin clots are relatively resistant to lysis. In acute ICH, fibrin clots are more susceptible to tissue plasminogen activator–mediated lysis compared with in IS, which might affect ICH pathogenesis. (Stroke. 2012;43:1412-1414.)

Key Words: fibrin clot ■ fibrinolysis

The significance of fibrin clot in acute stroke depends on stroke type. In intracerebral hemorrhage (ICH), it is crucial to stop bleeding, whereas in ischemic stroke (IS), this is highly undesirable. Abnormalities in fibrin clot generation and stabilization influence the risk for both ICH and IS. We showed previously that fibrin clot properties in acute IS are unfavorably altered.\(^1\) What happens in acute ICH remains unknown. Thus, we studied the clot properties in acute ICH in relation to clinical and hematoma parameters.

Subjects and Methods
We enrolled consecutive acute ICH patients admitted within 12 hours after stroke onset. Subjects with acute illness, malignancy, hepatic or renal dysfunction, recent acute coronary syndrome (<6 months), or who were on oral anticoagulants, heparins, or clopidogrel were excluded. Two control groups were recruited: acute IS patients sampled within 24 hours after stroke onset, and nonstroke controls.

The study was approved by the University Ethical Committee. All participants gave informed consent.

Stroke work-up was performed as previously described.\(^1,2\) ICH patients had an additional computed tomography scan 24 to 72 hours after disease onset and angio-computed tomography imaging. Hematoma volumes were calculated by the ABC/2 method.\(^3\) Hemorrhage location was defined as lobar or nonlobar.\(^2\)

Demographics and clinical data were collected using a standardized questionnaire. Risk factors were defined as previously described.\(^1\)

Lipid profile, albumin, creatinine, glucose, fibrinogen, tissue plasminogen activator antigen, plasminogen activator inhibitor-1 antigen, and D-dimer levels were determined as previously described.\(^1\) Venous blood samples for fibrin analysis were managed as previously described.\(^4\) A set of plasma fibrin clot variables: permeability coefficient (\( K_s \)), lysis time (\( t_{50\%} \)), maximum D-dimer levels (\( D_{max} \)), maximum rate of D-dimer release in the perfusion assay and using turbidimetry (\( D_{in} \)), and lag phase and maximum absorbance of fibrin gels at 405 nm (\( \Delta A_{max} \)) were analyzed.\(^4\) Fifteen ICH patients had repeat blood studies on discharge.

The \( \chi^2 \) test, Fisher exact test, Mann-Whitney \( U \) test, or Student test were used as appropriate. Correlations were assessed by the Spearman or Pearson tests as indicated. Probability value \(<0.05\) was considered significant. For testing difference between groups adjusted for age and fibrinogen level, the general linear model procedure was used with Bonferroni correction. Probability value \(<0.001\) was considered significant.

The study was powered to have a 80\% chance to detect the 10\% difference between groups at the 0.05 significance level: for \( K_s \), 45 subjects per group were needed, and for \( t_{50\%}, 32 \) subjects were needed.\(^4\)

Results
Baseline characteristics of study subjects are summarized in Table 1. Nonlobar hemorrhage location was in 67.3\% of ICH patients.

The median National Institutes of Health Stroke Scale score in ICH patients on admission was 7 (interquartile range
[IQR], 3–15), whereas on discharge (22±7 days after stroke; range, 14–43 days) in 43 survivals, the score was 4 (IQR, 1–9). Six patients died because of neurological complications. Median hematoma volume on admission was 14.23 cm³ (IQR, 4.42–28.65) in a whole ICH group, 22.06 cm³ (IQR, 12.10–52.80) among lobar, and 9.36 cm³ (IQR, 2.74–19.33) among nonlobar hemorrhages.

Fibrin clot properties are presented in Table 2. Compared with nonstroke controls, after adjustment for age and fibrinogen levels, both acute stroke groups had prolonged $t_{50\%}$, higher $\Delta A_{\text{Abs}_{\text{max}}}$, and lower $K_s$. The $D-D_{\text{rate}}$ was significantly lower only in IS patients. Comparing ICH and IS groups, after adjustment for age and fibrinogen levels, only $t_{50\%}$ differed significantly (13% shorter in ICH; $P<0.001$).

### Table 1. Characteristics of Studied Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Acute Intracerebral Hemorrhage (n=49)</th>
<th>Acute Ischemic Stroke (n=52)</th>
<th>Non-Stroke Controls (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69.6±11.4</td>
<td>69.0±11.8</td>
<td>65.9±6.2</td>
</tr>
<tr>
<td>Female</td>
<td>44.9</td>
<td>42.3</td>
<td>40.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>79.6</td>
<td>69.2</td>
<td>62.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28.6</td>
<td>32.7</td>
<td>6.0†‡</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>20.4</td>
<td>28.8</td>
<td>10.0‡</td>
</tr>
<tr>
<td>Smoking</td>
<td>8.2</td>
<td>21.2</td>
<td>42.0†‡</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.6</td>
<td>23.1</td>
<td>8.0†</td>
</tr>
<tr>
<td>Aspirin</td>
<td>20.4</td>
<td>90.4*†‡</td>
<td>28.0†‡</td>
</tr>
<tr>
<td>Statins</td>
<td>57.1</td>
<td>59.6</td>
<td>26.0†‡</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.89±1.59</td>
<td>4.31±1.64</td>
<td>2.61±0.45††</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>7.01±2.33</td>
<td>6.73±2.47*</td>
<td>5.04±0.66††</td>
</tr>
<tr>
<td>Creatinine, umol/L</td>
<td>96.96±121.2</td>
<td>77.71±25.6*</td>
<td>74±11.64</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.27±1.37</td>
<td>5.3±2.05</td>
<td>5.31±1.14</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.47±0.45</td>
<td>1.34±0.34</td>
<td>1.40±0.34</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>3.14±1.22</td>
<td>3.27±1.19</td>
<td>3.33±0.96</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.36±0.71</td>
<td>1.54±2.43*†‡</td>
<td>1.31±0.50</td>
</tr>
<tr>
<td>tPA, ng/mL</td>
<td>12.44±2.64</td>
<td>15.15±3.15*§</td>
<td>9.91±3.51†‡</td>
</tr>
<tr>
<td>PAI-1, ng/mL</td>
<td>19.84±6.93</td>
<td>24.94±6.46*§</td>
<td>12.54±4.04‡</td>
</tr>
</tbody>
</table>

Values are presented as percentages or mean±SD.

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; tPA, tissue plasminogen activator; PAI-1, Plasminogen Activator Inhibitor-1.

*P<0.05 ICH vs IS.
†P<0.05 ICH vs controls.
‡P<0.05 IS vs controls.

### Table 2. Fibrin Structure and Function Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Acute Intracerebral Hemorrhage (n=49)</th>
<th>Acute Ischemic Stroke (n=52)</th>
<th>Non-Stroke Controls (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_s$, 10^-9 cm²</td>
<td>6.52±1.12</td>
<td>6.00±1.16*</td>
<td>8.11±1.08†‡</td>
</tr>
<tr>
<td>$t_{50%}$, min</td>
<td>9.23±1.27</td>
<td>10.62±1.31*§</td>
<td>7.66±1.23†‡</td>
</tr>
<tr>
<td>D-D_{max}, mg/L</td>
<td>4.21±0.80</td>
<td>4.49±0.61*§</td>
<td>3.81±0.44†‡</td>
</tr>
<tr>
<td>D-D_{rate}, mg/L/min</td>
<td>0.072 (0.066–0.079)</td>
<td>0.069 (0.061–0.073)*</td>
<td>0.079 (0.075–0.084)†‡</td>
</tr>
<tr>
<td>$\Delta A_{\text{Abs}_{\text{max}}}$, 405nm</td>
<td>0.88±0.08</td>
<td>0.92±0.11*</td>
<td>0.77±0.04†‡</td>
</tr>
<tr>
<td>Lag phase, s</td>
<td>42.14±5.15</td>
<td>43.23±4.51</td>
<td>44.20±4.19</td>
</tr>
<tr>
<td>Compaction, %</td>
<td>50.16±5.25</td>
<td>49.23±7.18</td>
<td>54.39±5.31†‡</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or median (interquartile range).

$K_s$ indicates permeability coefficient; $t_{50\%}$, lysis time; D-D_{max}, maximum D-dimer levels in the lysis assay; D-D_{rate}, maximum rate of D-dimer release in the lysis assay; $\Delta A_{\text{Abs}_{\text{max}}}$, maximum absorbance of fibrin gel at 405 nm determined by using turbidimetry.

*P<0.001 ICH vs IS.
†P<0.001 ICH vs controls.
‡P<0.001 IS vs controls.
§P<0.001 ICH vs IS patients adjusted for age and fibrinogen.
¶P<0.001 ICH vs controls adjusted for age and fibrinogen.

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In ICH patients, only compaction and $d_{\text{rate}} - d_{\text{max}}$ correlated with neurological deficit measured by the National Institutes of Health Stroke Scale on admission and at discharge ($R = 0.34$ and $R = 0.35$, respectively; $P < 0.05$). $d_{\text{rate}} - d_{\text{max}}$ correlated with modified Rankin Scale at discharge ($R = 0.30$; $P < 0.05$). Hematoma volume on admission correlated with lag phase ($R = -0.33$; $P < 0.05$) and compaction ($R = 0.31$; $P < 0.05$). No correlations were found between fibrin clot parameters and the difference between hematoma volume measured on admission and 24 to 72 hours later. At discharge, we observed a reduction in fibrinogen levels (from $3.89 \pm 1.59$ g/L to $2.77 \pm 0.36$ g/L; $P < 0.05$) and in clot compaction (from $50.16\% \pm 5.25\%$ to $45.53\% \pm 3.42\%$; $P < 0.01$). The remaining fibrin clot variables were unchanged.

Patients with lobar and nonlobar hemorrhages were similar in respect to studied parameters (data not shown).

Discussion

We found that fibrin clot properties in acute ICH are altered in comparison with those in nonstroke subjects. We also confirmed our previous results regarding acute IS.1 The pattern of observed changes in both acute strokes was similar; that raises a question on specificity of fibrin clot abnormalities noted in different vascular pathologies.1,5,6

We investigated 2 acute conditions, ICH and IS, in which inflammation and oxidative stress are crucial.7,8 Proinflammatory cytokines increase fibrin clot resistance to fibrinolysis,9 and in acute coronary syndrome, the altered clot properties correlated with markers of inflammation and oxidative stress.5

In acute ICH, faster clot formation and greater resistance to lysis are desirable. However, the hypothesis that altered fibrin clot characteristics reflect an immediate response to the vessel rupture and blood leakage seems unconvincing. First, why did protective properties of fibrin clot appear so selectively only in cerebral hemorrhage? Second, among analyzed parameters, only lag phase and compaction correlated with hematoma volume. The first parameter showed a rather unexpected negative correlation: faster clot formation, but larger hematoma. A positive correlation between compaction and hemorrhage extension is more pathophysiologically relevant, given that low compaction is related to reduced lysis.10

Positive correlations between neurological deficit and compaction and $d_{\text{rate}} - d_{\text{max}}$ were similar to those observed in IS.1

There are limitations to this study. First, there are a limited number of participants; however, the study is adequately powered. Second, there was not perfect matching for comorbidities, risk factors, or treatment, with an overrepresentation of smokers among controls. However, smoking is related to faster formation and more resistant fibrin clots11; thus, more smokers among controls would blunt the results. Third, differences in clot permeability were not supported by scanning electron microscopy.

In conclusion, both acute ICH and IS are associated with altered fibrin clot parameters. More efficient degradation of fibrin clots characterizes hemorrhagic stroke, which might be important in ICH pathophysiology.

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Disclosures

None.

References

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