Background and Purpose: Intracerebral hematoma may complicate treatment of acute myocardial infarction in patients treated with fibrinolytic agents. We studied the clinical presentation and computed tomographic characteristics.

Methods: We studied eight patients with lobar intracerebral hematomas after fibrinolytic treatment of acute coronary occlusion. All patients had electrocardiographic and laboratory evidence of acute myocardial infarction and were treated with tissue plasminogen activator or streptokinase followed by heparin infusion to prevent reocclusion. Computed tomography scans of 17 patients with cerebral hemorrhage from other causes were used for comparison.

Results: For most patients, outcome was fatal within hours of the ictus. Computed tomography scans showed superficially large lobar hematomas in six patients. One patient had a putaminal hemorrhage, and one had a vermis hemorrhage. Multiple sites of intracerebral hemorrhage were noted in three patients. Fluid levels inside the hematoma suggesting continuing hemorrhage into multiple compartments were common. Radiologically, fluid levels in hematomas, multiple hematomas, and blood in multiple compartments served to differentiate fibrinolysis-induced hemorrhage from hemorrhage of other causes. Severe amyloid angiopathy was found in one patient who was operated on.

Conclusions: Hemorrhages in multiple compartments and the presence of fluid levels inside the hematoma suggest fibrinolysis-associated cerebral hematomas. Severe amyloid angiopathy may be a crucial factor in this clinical entity. Outcome is poor, and a high proportion of patients have rapid progression to brain death. Therefore, emergency neurosurgical evacuation will probably be unsuccessful.

(Stroke 1993;24:554-557)

KEY WORDS • fibrinogen • cerebral hemorrhage • myocardial infarction

Fibrinolytic therapy in the management of acute myocardial infarction is beneficial only when begun early.1-3 A significant threat is intracerebral hemorrhage. There is some evidence of an increased frequency in patients with systemic hypertension on admission,4 but the location of the intracerebral hemorrhages does not fit with the typical ganglionic site of hypertension-associated intracerebral hemorrhages. Intracerebral hematoma may also be more common in elderly patients, but statistical validation of differences in frequency has been limited by the small number of patients. Two recent case reports, however, have implied that fibrinolysis-associated intracerebral hemorrhage may have its origin in amyloid angiopathy.5,6

None of the earlier studies of computed tomography (CT) scan characteristics in hematomas associated with tissue plasminogen activator compared findings with those from other causes of intracerebral hemorrhage.

We report clinical and radiographic characteristics of eight cases of intracerebral hemorrhage after fibrinolytic therapy in patients with acute myocardial infarction. CT scan patterns in 17 patients with cerebral hemorrhage from other (proven) causes were used for comparison.

Subjects and Methods
We reviewed a personal series of eight patients with myocardial infarction and intracerebral hemorrhage associated with tissue plasminogen activator. In addition, from the Mayo Clinic record system we retrieved the records of 17 age-matched patients with intracerebral hemorrhage and pathologically proven brain metastasis or amyloid or arteriovenous malformations demonstrated by angiography.

Results
Details on the eight patients are given in Table 1. All patients had electrocardiographic and laboratory evidence of acute myocardial infarction. None of the patients had a history of a recent stroke. Most patients were normotensive on admission. All patients were treated with additional heparin infusion to prevent reocclusion of the coronary arteries. All patients presented with sudden hemiparesis, aphasia, agnosia, or a combination of signs. Level of consciousness rapidly decreased in all patients after onset of focal signs except patient 7, who had a small putaminal hematoma.

The onset of neurological signs and symptoms ranged from 30 minutes to 48 hours after intravenous adminis-
TABLE 1. Clinical Features of Eight Patients With Intracerebral Hematomas After Fibrinolytic Therapy

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>MI location</th>
<th>Rx (dose)</th>
<th>Hx of HT</th>
<th>BP on admission (mm Hg)</th>
<th>PT/APTT* (seconds)</th>
<th>Time between first Sx and thrombolysis (hours)</th>
<th>CT scan localization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/72/M</td>
<td>Anterior</td>
<td>SK (1.5 MU)</td>
<td>No</td>
<td>140/70</td>
<td>11.5/95.6</td>
<td>48</td>
<td>Multiple, SAH, IVH, SDH</td>
<td>Severely disabled; died from sepsis</td>
</tr>
<tr>
<td>2/69/F</td>
<td>Anterolateral</td>
<td>SK (1.5 MU)</td>
<td>Yes</td>
<td>120/70</td>
<td>NA/&gt;120</td>
<td>14</td>
<td>Multiple</td>
<td>Brain death within 2 hours</td>
</tr>
<tr>
<td>3/75/M</td>
<td>Inferior</td>
<td>SK (1.5 MU)</td>
<td>No</td>
<td>140/70</td>
<td>11.9/25.2</td>
<td>12</td>
<td>Multiple, IVH, SAH</td>
<td>Brain death within 2 hours</td>
</tr>
<tr>
<td>4/70/M</td>
<td>Inferolateral</td>
<td>t-PA (100 mg)</td>
<td>Yes</td>
<td>170/100</td>
<td>12.0/134</td>
<td>27</td>
<td>R temporoparietal, IVH, SAH</td>
<td>Brain death in 24 hours</td>
</tr>
<tr>
<td>5/72/F</td>
<td>Lateral</td>
<td>t-PA (100 mg)</td>
<td>No</td>
<td>140/90</td>
<td>12.5/31.3</td>
<td>1/2</td>
<td>L frontoparietal, IVH</td>
<td>Brain death within 2 hours</td>
</tr>
<tr>
<td>6/62/M</td>
<td>Inferior</td>
<td>t-PA (150 mg)</td>
<td>No</td>
<td>130/80</td>
<td>NA/&gt;150</td>
<td>15</td>
<td>R frontal, IVH, SAH</td>
<td>Brain death within 2 hours</td>
</tr>
<tr>
<td>7/61/F</td>
<td>Inferolateral</td>
<td>t-PA (100 mg)</td>
<td>No</td>
<td>110/85</td>
<td>12.7/23.7</td>
<td>8</td>
<td>R putamen</td>
<td>Good recovery</td>
</tr>
<tr>
<td>8/70/M</td>
<td>Inferior</td>
<td>t-PA (150 mg)</td>
<td>No</td>
<td>140/80</td>
<td>11.7/34.5</td>
<td>6</td>
<td>Vermis, SAH</td>
<td>Brain death within 2 hours</td>
</tr>
</tbody>
</table>

APTT, activated partial thromboplastin time; BP, blood pressure; CT, computed tomography; HT, hypertension; Hx, history; IVH, intraventricular hemorrhage; L, left; MI, myocardial infarction; MU, megaunits; NA, not available; Pt, patient; PT, prothrombin time; R, right; Rx, treatment; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; SK, streptokinase; Sx, symptoms; t-PA, tissue plasminogen activator.

*Normal values: PT, 10.9–12.8 seconds for both sexes; APTT, 26–41 seconds, male, and 25–38 seconds, female.

Comparison between fibrinolysis-associated hematomas and other types of intracerebral hematomas revealed that fluid levels inside the hematomas suggesting continuing or repeated hemorrhage were more frequently found in fibrinolysis-associated hematomas (Table 2). Patients with fibrinolysis-associated hemorrhage more often had multiple parenchymal hematomas as well as hematomas in multiple intracranial compartments (intraventricular, subarachnoid, subdural, and parenchymal). In 75% of the patients with...
fibrinolysis-associated hemorrhages but in none of those with other types of hemorrhages, CT scan showed evidence of blood in three or more compartments. All other CT scan characteristics were evenly distributed among the four types of intracerebral hemorrhage (Table 2).

**Discussion**

This comparatively large series of patients with fibrinolysis-associated intracerebral hemorrhages emphasizes a few important clinical points.

First, the catastrophic clinical course of this subset of lobar intracerebral hemorrhage is illustrated. Large hemorrhages in multiple sites and compartments usually result in rapid evolution to brain death. Therefore, emergency clot evacuation is unlikely to lead to any significant neurological improvement. In patients with an initial small-volume hematoma, CT scanning probably should be repeated within 1 hour to assess progression of the hemorrhage, irrespective of the coagulation values. Our data suggest that bleeding may continue despite efforts to counteract heparinization and thrombolysis.

The pathogenesis of fibrinolysis-associated intracerebral hemorrhages can be understood only by either histopathological study or detailed analysis of the CT scan features and comparison with other well-established causes of hemorrhage into the brain parenchyma. A second major finding in this study, not emphasized in previous reports, is the relatively frequent occurrence of fluid levels inside the hematoma. Also noted was a higher frequency of bleeding in multiple compartments in patients with fibrinolysis therapy than in those with hemorrhage from other causes. The CT scan feature of fluid levels clearly suggests coagulopathy, presumably caused by persistent hypofibrinogenemia induced by a thrombolytic agent and heparinization. Heparinization is standard therapy in these patients to prevent reoclusion of the coronary artery.

The cause of lobar hemorrhage after fibrinolytic treatment remains puzzling. We speculate, but have proof in only one patient, that the presence of amyloid angiopathy may be an important risk factor. We cannot exclude the possibility, however, of hemorrhage into a prior silent infarction as the mechanism in some of these patients. Long-standing hypertension has been specifically implicated as a risk factor for cerebral hemorrhage. However, the site of hemorrhage associated with hypertension is usually in the distribution of perforating vessels, not lobar. Patients with hypertension alone usually have bleeding into sites such as basal ganglionic, posterior lateral thalamus, pons, and cere-

![FIGURE 2](https://stroke.ahajournals.org/)

**FIGURE 2.** Sequential computed tomography scans in patient 6. Left panel: Immediately after onset of hemiparesis. Right panel: Extension of hemorrhage and fluid level 1 hour later.

<table>
<thead>
<tr>
<th>CT scan characteristics*</th>
<th>t-PA (n=17)</th>
<th>AVM (n=5)</th>
<th>Tumor† (n=5)</th>
<th>Amyloid (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Multiple</td>
<td>3</td>
<td>37</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IVH</td>
<td>6</td>
<td>75</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>SAH</td>
<td>5</td>
<td>63</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral</td>
<td>13</td>
<td>76</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>Central</td>
<td>4</td>
<td>24</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Fluid levels</td>
<td>10</td>
<td>59</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Lobulated</td>
<td>5</td>
<td>29</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spherical</td>
<td>12</td>
<td>71</td>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>

CT, computed tomography; t-PA, tissue plasminogen activator; AVM, arteriovenous malformation; n, number of hemorrhages; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.

*Size (cm): t-PA, 4.2; AVM, 5.4; tumor, 5.2; amyloid, 6.2.
†Histological features were adenocarcinoma (two), squamous cell carcinoma (two), and sarcoma (one).
‡Number of patients.
bellar hemispheres. Patients with hypertension and lobar hemorrhages may have amyloid angiopathy as well. One recent study of surgically treated patients with lobar hematomas indeed suggested that amyloid angiopathy is a major contributing factor. In two series of patients with lobar hemorrhage but without anticoagulant or fibrinolytic treatment, hypertension was found in only one third of the patients. Although hemorrhage into the cerebellum has traditionally been linked to hypertension, blood pressure was normal in our one patient with a massive vermis hemorrhage. Furthermore, one study claimed that vermis hemorrhages were relatively frequent in anticoagulated patients.

We suspect, therefore, that cerebral amyloid angiopathy may be a contributing, if not crucial, factor in fibrinolysis-associated hemorrhages. Intracerebral lobar hemorrhage is frequently associated with cerebral amyloid angiopathy in patients in the sixth or seventh decade of life. It encompasses multiple, usually superficially located, areas of hemorrhage on CT scans. Frontal or parietal lobe hemorrhages are common, but cerebellar and putaminal locations have been described in association with amyloid angiopathy. Recently, it was also noted that cerebral amyloid angiopathy associated with lobar intracerebral hemorrhage resulted in good outcome in the vast majority of patients. The overall devastating prognosis in our series, therefore, cannot be readily attributed to amyloid angiopathy alone.

We postulate that fibrinolysis-associated intracerebral hemorrhage in patients with acute myocardial infarction is associated with severe amyloid angiopathy. Treatment with tissue plasminogen activator and heparin may disturb the marginally compensated balance of clot-forming and clot-dissolving pathways. The multiplicity of hemorrhage and the presence of fluid levels inside the hematoma are compatible with this explanation and are both highly suggestive of fibrinolysis-associated hemorrhage.

Studies of patients with fibrinolysis-induced intracerebral hemorrhage in acute myocardial infarction have usually reported rates of 0.4–0.7%, the key to initiation of intracerebral hemorrhage in such a small proportion of patients remains unknown. In addition, whether combined treatment with thrombolytic agents and heparin rather than thrombolysis alone triggers the event is unclear.

Systematic neuropathological studies should focus on severe amyloid angiopathy in this subset of intracerebral hemorrhages.

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E F Wijdicks and C R Jack, Jr

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