Classification and Pathogenesis of Cerebral Hemorrhages After Thrombolysis in Ischemic Stroke

Paul Trouillas, MD; Rüdiger von Kummer, MD

Background and Purpose—Brain hemorrhage after ischemic stroke is a serious complication of treatment; however, its pathology is poorly understood. A classification based on brain imaging may help to better understand and avoid causal factors.

Methods—Review of the results of controlled randomized trials and the available literature.

Results—Hemorrhagic infarctions have no impact on clinical outcome and are probably not associated with the thrombolytic itself and the type of reperfusion strategy. They are associated with the extent of ischemic damage and most probably to an ischemic vasculopathy. Parenchymal hematomas are often clinically relevant. Their incidence is affected by the thrombolytic itself, the type, and probably the time point of reperfusion strategy. The loss of hemostatic control seems important in their pathogenesis. Extraischemic hematomas (remote from the infarct), unique or multiple, suggest pre-existing brain pathology, especially cerebral amyloid angiopathy.

Conclusions—The radiological description of 3 different types of brain hemorrhage is useful to better understand the specific pathology and the impact on clinical outcome. It may help to avoid clinically relevant brain hemorrhages.

Key Words: cerebral infarction • hemostasis • heparin • intracranial hemorrhage • thrombolysis
study, identifiable factors included severity at baseline and brain edema or mass effect by CT before treatment. In European Cooperative Acute Stroke Study 2 (ECASS2), factors of symptomatic ICH (SICH) were rt-PA, a history of congestive heart failure, extent of parenchymal hypoattenuation on baseline CT, and increasing age. Protocol violations have a probable relationship with SICH. In 15 open-label studies after approved indications and guidelines for t-PA use, the greatest rate was found in the study with the second highest proportion of protocol deviations; however, the ICH symptomatic rate was not statistically correlated with the frequency of protocol violations. In PROACT II, the only risk factor of symptomatic hemorrhage associated with intraarterial prourokinase was baseline hyperglycemia >200 mg/dL; a retrospective analysis showed that patients with poor baseline CT (ASPECTS ≤7) may have an increased rate of SICH. Post-thrombolytic unfractionated heparin was used in this study and might have played a role in the high rate of SICH.

The impact of symptomatic hemorraghes on the global mortality may be masked by other factors. In NINDS part 2, mortality associated with symptomatic hemorrhage was increased by a 10-fold factor in the rt-PA group (47%) when compared with the placebo group (4.7%). However, the global mortality was decreased in the rt-PA group (17% versus 21%) because of the decrease of nonhemorrhagic deaths.

From a clinical point of view, the distinction symptomatic versus nonsymptomatic hemorrhage, especially if precisely founded on criteria like those of Purlan et al, provides a basic tool for trials, allowing a useful assessment of the security and the efficacy related to the procedures and the drugs.

However, this distinction is not precise enough to allow a thorough pathophysiological analysis of the bleedings. Clinical deterioration during the follow-up of ischemic stroke may have a variety of causes like another ischemic stroke, decrease in cerebral perfusion pressure, and mass effect of ischemic edema. Depiction of cerebral blood by CT or MRI does not per se mean that it is responsible for clinical deterioration. Intracranial blood may have been present before clinical deterioration was assessed. It is unlikely that small amounts of blood in ischemic and consequently functionally dead brain tissue can affect the clinical status of the patient. Moreover, criteria that define blood on CT were seldom provided. Von Kummer has criticized the widespread use of the term “symptomatic hemorrhage,” without a careful analysis of other associated factors like ischemic edema and mass effect that might be the real cause of clinical deterioration, and not the hemorrhage itself. On the other hand, massive bleedings into “silent” areas of the brain may be asymptomatic or slightly symptomatic, but these same bleedings would be symptomatic in a strategic area.

The Anatomic–Radiological Distinction: Parenchymal Hemorrhage Versus Hemorrhagic Infarct

Pessin et al first proposed the distinction between hemorrhagic infarcts (HIs) and parenchymal hematomas (PHs) on the basis of the radiologic anatomy of the lesions. The

<table>
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<th>TABLE 1. Anatomic–Radiological Definitions of Cerebral Bleedings in NINDS and the ECASS Studies</th>
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<tr>
<td><strong>NINDS definitions</strong></td>
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<tr>
<td>HI: acute infarction with punctate or variable hypodensity/hyperdensity, with an indistinct border within the vascular territory</td>
</tr>
<tr>
<td>PH: typical homogeneous, hyperdense lesion with a sharp border with or without edema or mass effect</td>
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<tr>
<td><strong>ECASS (1 and 2) definitions</strong></td>
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<tr>
<td>HI: petechial infarction without space-occupying effect</td>
</tr>
<tr>
<td>HI1: small petechiae</td>
</tr>
<tr>
<td>HI2: more confluent petechiae</td>
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<tr>
<td>PH: hemorrhage (coagulum) with mass effect</td>
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<tr>
<td>PH1: &lt;30% of the infarcted area with mild space-occupying effect</td>
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<tr>
<td>PH2: &gt;30% of the infarcted area with significant space-occupying effect</td>
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NINDS rt-PA study group gave definitions for these 2 types of lesions (Table 1). The ECASS investigators discredited the concept of symptomatic hemorrhage and also categorized the post-thrombolytic hemorrhagic transformations according to radiographic criteria; these investigators proposed to use the distinction for HI (HI1 and HI2) and for PH (PH1 and PH2; Table 1), according to Pessin et al, that was later used for analysis. Actually, the American and European anatomic–radiological definitions do not really match. As shown in Table 1, the diagnosis of PH or HI does not take into account the mass effect in the NINDS definition; conversely, in the ECASS definition, HI never involves a mass effect, whereas PH (1 and 2) systematically involves a mass effect. Thus, discrepancies in the lesions studied by the NINDS and ECASS1 and ECASS2 exist, which might explain differences in assessing distinct predictive factors. For instance, HI on follow-up CT had a relatively low incidence in the NINDS rt-PA study. This may be explained by early treatment, although the time interval between stroke onset and treatment initiation appeared not to be associated with the incidence of brain hemorrhage. An alternative explanation is that NINDS investigators defined blood as an area on CT with higher x-ray attenuation than brain tissue, not taking into account blood intermixed with ischemic hypoattenuating tissue.

The NINDS, ECASS, and ATLANTIS investigators have pooled their data and used the ECASS PH2 definition in a combined analysis after re-evaluation of the hemorrhages. The anatomic–radiological definition was thus considered a relevant basis for pathophysiological research.

**Timing Distinction: Early (<24 hours) Versus Late (>24 hours) Cerebral Bleeding**

It must be noted that the time period to search for the bleeding is fundamental for pathophysiological studies. In several studies, the bleeding interval observed is 36 hours, whereas in others, all the bleedings that occurred within 7 days were studied. Because late lesions (>24 hours) are remote from thrombolysis and the initial hemodynamic status of the lesion, correlations with these events might be poorer. Moreover, in several trials, therapeutic factors such as oral or
TABLE 2. Clinic–Biological Differences Between Post-Thrombolytic Bleedings

<table>
<thead>
<tr>
<th>Statistical linkages</th>
<th>HI</th>
<th>PH</th>
<th>Extraschismic Hematoma</th>
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<tbody>
<tr>
<td>Baseline clinical severity</td>
<td>Yes</td>
<td>No</td>
<td>nk*</td>
</tr>
<tr>
<td>Early CT findings</td>
<td>Yes</td>
<td>No**nk</td>
<td>nk</td>
</tr>
<tr>
<td>Poor day 90 outcome</td>
<td>No</td>
<td>Yes nk</td>
<td>nk</td>
</tr>
<tr>
<td>rt-PA</td>
<td>No***</td>
<td>Yes</td>
<td>Probable nk</td>
</tr>
<tr>
<td>Previous aspirin</td>
<td>No</td>
<td>Yes nk</td>
<td>nk</td>
</tr>
<tr>
<td>FDP coagulopathy</td>
<td>No</td>
<td>Yes nk</td>
<td>nk</td>
</tr>
<tr>
<td>Recanalization</td>
<td>Early</td>
<td>Late</td>
<td>nk</td>
</tr>
</tbody>
</table>

*nk indicates not known; **except extent of hypoattenuation in ECASS2 and in NINDS (5); ***apparently, see Discussion.

intra-venous anticoagulants are authorized after the 24th hour and may superimpose their influence to the primary factors. A shorter post-thrombolytic interval, for instance <24 hours, is possibly able to better take into account the relationship between thrombolysis or the baseline status of the infarct and the bleeding process and to “enrich” the detection of causative factors.

HIIs: Clinical Outcome, Risk Factors, and Origin (Table 2)

There is overall agreement on the characterization of HI, as defined by the ECASS criteria: (1) HI has no significant impact on the outcome at 3 months in the ECASS1 and ECASS2 studies17,18; (2) HI is linked to the baseline stroke severity, a fact observed by Larrue et al10 in ECASS1 and in an open-label study21; (3) HI is linked to early CT changes16,21; (4) HI is statistically independent of rt-PA and actually has a lower incidence in rt-PA groups than in control groups of ECASS1 and ECASS28,16; and (5) preliminary data seem to indicate that HI is also independent of early fibrinogen coagulopathy,20,21 characterized by the increase of fibrinogen degradation products (FDPs) at 2 hours after the start of thrombolysis.

The lower incidence of HI in the rt-PA group compared with the placebo group in ECASS1 and ECASS28,16 may be explained by an acute conversion of HI into PH under the effect of rt-PA. Thus, the fact that HI is not related to the thrombolytic itself (and to its biological effects) has to be discussed. Repeated post-thrombolytic brain imaging might shed light on this issue.

It appears logical that larger ischemic brain lesions have an increased chance of HI because of their extent and the degree of ischemia. As a matter of fact, HI is related to factors indicative of the depth and size of baseline ischemia (i.e., baseline clinical severity and extent of ischemic edema visible on CT). Although this fact was not demonstrated specifically for HI, MRI studies have indicated that ischemic parameters were factors of hemorrhagic transformation, particularly a lower value of apparent diffusion coefficient.22–25 HIs may occur more often in patients with early reperfusion of ischemic brain tissue according to a transcranial Doppler (TCD) study.26

These observations support the view that hemorrhagic transformation of ischemic brain tissue is the natural course of ischemic brain injury. Thus, HI consists of a blood extravasation of limited amount and size, with persistence of the hemostasis control, and is most certainly attributable to an ischemic vasculopathy.27 The fact of a reperfusion vasculopathy has to be confirmed.

PHs: Clinical Outcome, Risk Factors, and Origin (Table 2)

There is also a general agreement about the characterization of PH: (1) PH definitely has a very significant impact on the outcome at 3 months in the ECASS1 and ECASS2 studies, particularly PH22,16–18; (2) baseline clinical severity is not a factor of PH in the studies based on the ECASS definition8,16,20; (3) violations of protocols and endorsements to guidelines are factors14,15; (4) age appears as a weak factor in ECASS16 and ECASS28; (5) baseline CT findings are not factors in ECASS1,16 but extent of parenchymal haemorrhage on CT is a factor in ECASS28 and NINDS5; (6) on the hemostasis side, PH appears as strongly statistically linked to rt-PA in ECASS1 (odds ratio [OR], 3.6; 95% CI, 2.6 to 6.1),16 ECASS2 (OR, 3.61; 95% CI, 1.78 to 7.31),8 and in the combined analysis of ATLANTIS, ECASS, and NINDS study rt-PA stroke trials19; moreover, PH is linked to post-thrombolysis use of aspirin;20 (7) unfractionated heparin is a probable factor of PH in intra-arterial thrombolysis of middle cerebral artery thrombosis stroke27; and (8) high molecular weight heparin during the first 24 hours is a factor of PH because the PH rate was increased in ECASS29,15 (high-molecular-weight heparin allowed during this time) when compared with ECASS1 and NINDS, in which heparin was excluded during the 24 first hours.9 Preliminary data20 seem to indicate that PH is statistically linked to rt-PA–induced early fibrinogen degradation coagulopathy, involving an increase in FDPs at 2 hours attributable to a lack of fibrin specificity and a direct attack of circulating fibrinogen. Early increase of FDP has also been demonstrated to be a factor of cerebral PH in MI thrombolysiss28,29 because of specific fibrinogen fragments.30,31 It has also been shown, in MI thrombolysis, that streptokinase yields an unacceptable frequency of post-thrombolytic PH in cerebral thrombolysis.32 Another causal factor of PH might be delayed post-thrombolytic reperfusion (>6 hours) according to a TCD study,26 suggesting that progressive ischemic vasculopathy is less able to tolerate increases in perfusion pressure. However, the association between the delay of thrombolytic therapy and the incidence of PH seems less clear.19

The possibility of an acute conversion from HI into PH with thrombolysis raises the problem of the respective role of ischemia and thrombolysis in the creation of PH; the degree
of ischemia, in addition to the effect of the thrombolytic, might play a role.

The respective influence of ischemic and hemostatic factors for PH induction in cerebral thrombolysis is relatively straightforward. Cerebral ischemia increases the risk of PH by a factor of 12, as shown by the comparison of the hematoma incidence between MI rt-PA thrombolysis (0.53%)\(^2\) and cerebral rt-PA thrombolysis (6.4%).\(^4\) But once cerebral ischemia is present, the type of thrombolytic agent, as well as the dose, govern the basic risk of PH; streptokinase at a dose of 1 500 000 UI increases the odds of PH by 5.9,\(^3\) rt-PA 1.1 mg/kg by 3.6,\(^1\) and rt-PA 0.9 mg/kg by 3.\(^4\) In the DIAS study using low-dose desmoteplase, the OR of hematoma seems \(\approx 1.\)\(^3\) Thus, in acute cerebral infarcts, the thrombolytic drug and its dose are key predictive factors besides the vulnerability of the brain.

In conclusion, PH is a large extravasation of blood, possibly initiated by the ischemic lesion (and possibly to its late reperfusion into severely injured brain tissue) but clearly linked to the thrombolytic drug itself, to its biological effects and to a loss of the hemostatic control; it is also related to the nature and the dose of the thrombolytic drug.

A “Type 3” Post-Thrombolytic Hemorrhage: Extraischemic Hematomas (Table 2)

Although any hematoma, according to the ECASS criteria, should have a mass effect, there are extraischemic remote hematomas, possibly multifocal in nature with and without mass effect (Figure). These hemorrhages occur on CT in brain region without visible ischemic damage, that is remote from an ischemic infarct or in brains without visible ischemic lesion on CT.

The multifocal subtype of hematoma has been described in MI thrombolysis.\(^2\)\(^9\)–\(^3\)\(^7\) One kind of these lesions is related to general causes:\(^3\) leukemia, and other blood dyscrasias, neoplasms, vasculitis, and venous sinus thrombosis. Another kind is related to structural abnormalities of the vessels: arteriovenous malformations\(^3\)\(^8\)–\(^3\)\(^9\) and cerebral amyloid angiopathy (CAA).\(^3\)\(^7\)–\(^4\)\(^0\) Quantitatively, multifocal hematomas represent 15% to 38% of the ICH in MI thrombolysis.\(^2\)\(^8\)–\(^3\)\(^7\)

In acute stroke thrombolysis, the etiological spectrum for this extraischemic hematoma (unique or multifocal) may be identical. General causes, especially coagulopathies, may be involved. Structural vascular abnormalities are also possible; hypertensive angiopathy and angiopathy linked to gradient echo positive microbleeds\(^4\)\(^2\)–\(^4\)\(^3\) are candidates; cases of CAA are also probable\(^4\) because transgenic mice with CAA features (APP23) show a particular hemorrhagic sensitivity to rt-PA thrombolysis.\(^4\)\(^5\) Until now, it is clear that arterial aneurysms have not appeared as a cause of multiple bleeding.

Extraischemic cerebral hematomas (multifocal or not) have an incidence of 1.3% in the NINDS series.\(^5\) In the ECASS1 and ECASS2 studies, the incidence of brain hemorraghes in regions without visible ischemic tissue changes was 23 of 620 (3.7%) and 16 of 800 (2.0%), respectively (von Kummer, personal communication, 2005). The multifocal form of extraischemic PHs represent only 9% of all PHs, with a general risk of 0.6%.\(^4\)\(^6\)

Extraischemic multifocal hematoma after intravenous thrombolysis with rt-PA in a 53-year-old man with MI. Magnetic resonance tomography (data not shown) detected multiple hemosiderine deposits typical for CAA later. The patient survived with cognitive deficits.

Although calculations are not available, there is a high probability that these hematomas, like PH, are statistically linked to rt-PA.

Consequences for Analysis and Prevention

The fact that PH and HI, according to the ECASS definitions, show distinct clinical, etiological and biological significances confirms a posteriori the discriminating value of these definitions.

On the clinical side, the basic biological difference between post-thrombolytic bleedings might have simple and robust clinical consequences. HI is benign, associated with the natural course of ischemic brain infarctions, and probably not linked to hemostasis; no specific prevention is required. PH, immediately symptomatic or not, is a serious pathology (especially PH2) and is linked to hemostasis; a prevention is necessary, which would include a monitoring of coagulation.

In practical terms, the following recommendations can be given for the prevention of PH. The procedure excluding low molecular weight heparin during the 24 first hours after intravenous thrombolysis must strictly be followed. Unfractionated heparin immediately after intra-arterial thrombolysis should probably be avoided (however, only a randomized controlled study could found firmly this recommendation). Hemostasis analysis before thrombolysis and at 2 hours after the start of thrombolysis, with blood count and assay of fibrinogen and fibrin(ogen) degradation factors, is useful.
One of us recommends\(^3\) that patients with FDP > 100 mg/L 2 hours after start of thrombolysis should not have any anticoagulant for 72 hours. In the future, preventive manipulation of hemostasis with antithrombin antiproteases may be proposed in case of post-thrombolytic coagulopathy. Assessment of symptomatic brain hemorhages requires a radiological description of space occupying intracranial hematoma, the exclusion of intracranial pathology that could be responsible for clinical deteriorations before hemorrhage, and clinical deterioration by > 3 points of the NIHSS. The therapeutic impact of MRI findings require further study.\(^4\)\(^5\) Extrinsic hemorrhages probably share the etiologic status and therapeutic approaches of PH.

Another type of prevention might be to use, in the future, new doses of rt-PA (possibly lower) or new thrombolytic drugs, with a still a higher fibrin specificity and a less frequent attack of circulating fibrinogen. The fact that low-dose desmopressin induced an extremely low rate of hemorrhagic complications in the DIAS study\(^3\) must be taken into account.

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References


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