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

Cerebral hemorrhage is the most feared complication of intra-arterial or intravenous thrombolysis after ischemic stroke. Such hemorrhages are also a major complication of intravenous thrombolysis in myocardial infarction (MI), although less frequent. Some of these hemorrhages have a devastating prognosis in these 2 situations. Thus, it is of major importance to characterize the relevant nosologic distinctions, to better understand the intimate mechanisms, and to make proposals for prevention. Many answers are presently unknown concerning the ultimate factors of hemorrhage, and alternative explanations may be proposed for several issues.

In Search of a Pathophysiologically Relevant Classification of Cerebral Hemorrhages After Ischemic Stroke

The Clinical Distinction: Symptomatic Versus Nonsymptomatic Cerebral Hemorrhage

As early as 1976, Hanaway et al1 mentioned sudden clinical deteriorations after intravenous urokinase leading to death that corresponded to cerebral hemorrhage at autopsy. The introduction of computed tomography (CT) allowed a more timely correlation between the clinical state and cerebral pathology. In a report by von Kummer and Hacke2 concerning an intravenous dose of 100 mg of recombinant tissue plasminogen activator (rt-PA), 9% of patients had a fatal cerebral hemorrhage on CT.

Levy et al3 presented the concept of “symptomatic hemorrhage” when reporting the National Institutes of Health open-label study of rt-PA. It is defined as a “contemporaneous neurological worsening” with blood on the CT image; of 94 patients, 5 presented with this phenomenon. In the report of the National Institute of Neurological Disorders and Stroke (NINDS) controlled study, symptomatic cerebral hemorrhages are described in parts 1 and 2, with the following definition: “any CT-documented hemorrhage that was temporally related to deterioration in the patient’s clinical condition in the judgment of the clinical investigator”; moreover, only hemorrhages occurring within 36 hours from treatment onset were taken into account.4,5 The PROACT II study6,7 provided for the first time a criterion for clinical deterioration and defined symptomatic hemorrhages as “an increase of 4 or more points in the NIHSS score in comparison with the preangiography score, within 36 hours from treatment initiation associated with any intracranial blood on CT.”

Risk factors of symptomatic intracerebral hemorrhages (ICHs) have been searched for, regardless of the anatomic–radiological nature of the bleeding. In the NINDS rt-PA
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 hypodensity 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 hemorrhages 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.4,5

From a clinical point of view, the distinction symptomatic versus nonsymptomatic hemorrhage, especially if precisely founded on criteria like those of Purlan et al,6 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 may have a variety of causes like another ischemic stroke, blood as an area on CT with higher x-ray attenuation than brain tissue, not taking into account blood intermixed with ischemic hypodensifying tissue. Interpretation on baseline CT, and increasing age.

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. An alternative explanation is that NINDS investigators defined PH as an area on CT with higher x-ray attenuation than brain tissue, not taking into account blood intermixed with ischemic hypodensifying tissue.

The 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,13 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 PH as an area on CT with higher x-ray attenuation than brain tissue, not taking into account blood intermixed with ischemic hypodensifying 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.16 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 1. Anatomic–Radiological Definitions of Cerebral Bleedings in NINDS and the ECASS Studies**

<table>
<thead>
<tr>
<th>Definition</th>
<th>NINDS definitions</th>
<th>ECASS (1 and 2) definitions</th>
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<tbody>
<tr>
<td>HI:</td>
<td>Acute infarction with punctate or variable hypodensity/hyperdensity, with an indistinct border within the vascular territory</td>
<td>HI: petechial infarction without space-occupying effect</td>
</tr>
<tr>
<td>PH:</td>
<td>Typical homogeneous, hyperdense lesion with a sharp border with or without edema or mass effect</td>
<td>HI1: small petechiae</td>
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<td></td>
<td></td>
<td>HI2: more confluent petechiae</td>
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HI: petechial infarction without space-occupying effect
PH: hemorrhage (coagulum) with mass effect

PH1: <30% of the infarcted area with mild space-occupying effect
PH2: >30% of the infarcted area with significant space-occupying effect

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.

**The Anatomic–Radiological Distinction: Parenchymal Hemorrhage Versus Hemorrhagic Infarct**

Pessin et al13 first proposed the distinction between hemorrhagic infarcts (HI) and parenchymal hematomas (PH) on the basis of the radiologic anatomy of the lesions. The
intravenous 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.

**HIs: 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 al19 in ECASS1 and in an open-label study20; (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 groups16,20; (5) preliminary data seem to indicate that HI is also independent of early fibrinogen coagulopathy20,21 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 ECASS216,18 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 (ie, 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 coefficient22–25 HI may occur more often in patients with early reperfusion of ischemic brain tissue according to a transcranial Doppler (TCD) study26.

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 vasculopathy27. 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 PH216–18; (2) baseline clinical severity is not a factor of PH in the studies based on the ECASS definition16,20; (3) violations of protocols and endorsements to guidelines are factors14,15; (4) age appears as a weak factor in ECASS1 and ECASS2; (5) baseline CT findings are not factors in ECASS1, but extent of parenchymal hypodensity is a factor in ECASS2 and NINDS; (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 prethrombolysis use of aspirin; (7) unfractionated heparin is a probable factor of PH in intra-arterial thrombolysis of middle cerebral artery thrombosis stroke17; and (8) high molecular weight heparin during the first 24 hours is a factor of PH because the PH rate was increased in ECASS215 (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 cerebroph PH in MI thrombolysis28,29 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, 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%)\(^28\) 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,\(^32\) rt-PA 1.1 mg/kg by 3.6,\(^16\) and rt-PA 0.9 mg/kg by 3.\(^4\) In the DIAS study using low-dose desmoteplase, the OR of hematoma seems \(\approx 1.\)\(^11\) 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.\(^28,34^-37\) One kind of these lesions is related to general causes:\(^37\) leukemias and other blood dyscrasias, neoplasms, vasculitis, and venous sinus thrombosis. Another kind is related to structural abnormalities of the vessels: arteriovenous malformations\(^38,39\) and cerebral amyloid angiopathy (CAA).\(^17,40,41\) Quantitatively, multifocal hematomas represent 15% to 38% of the ICH in MI thrombolysis.\(^28,34^-37\)

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\(^42,43\) are candidates; cases of CAA are also probable because transgenic mice with CAA features (APP23) show a particular hemorrhagic sensitivity to rt-PA thrombolysis.\(^45\) 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.\(^3\) In the ECASS1 and ECASS2 studies, the incidence of brain hemorrhages 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%.\(^46\)

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\textsuperscript{20} 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 antithrombotic antiproteases may be proposed in case of post-thrombotic coagulopathy. Assessment of symptomatic brain hemorrhages 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.\textsuperscript{42,43} Extraischemic hematomas 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\textsuperscript{35} must be taken into account.

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