Imaging-Based Decision Making in Thrombolytic Therapy for Ischemic Stroke
Present Status

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Background—Thrombolysis is the treatment of choice for acute stroke within 3 hours after symptom onset. Treatment beyond the 3-hour time window has not been shown to be effective in any single trial; however, meta-analyses suggest a somewhat lesser but still significant effect within 3 to 6 hours after stroke. It seems reasonable to apply improved selection criteria that allow differentiation between patients with and without a relevant indication for thrombolytic therapy.

Summary of Review—The present literature on imaging in stroke has been thoroughly reviewed, covering Doppler ultrasound (DU), arteriography, CT, and MRI and including modern techniques such as perfusion CT, diffusion- and perfusion-weighted MRI (DWI, PWI), CT angiography and MR angiography (CTA, MRA), and CTA source image analysis (CTA-SI). The authors present their view of a comprehensive diagnostic approach to acute stroke, which challenges the concept of a rigid therapeutic time window.

Conclusions—Information about the presence or absence of a vessel occlusion, whether by means of DU, CTA, or MRA, is essential before recombinant tissue plasminogen activator is given in the 3- to 6-hour time window. Clear demarcation of the irreversibly damaged infarct core and the ischemic but still viable and thus salvageable tissue at risk of infarction as seen on DWI/PWI/MRA or alternatively CT/CTA/CTA-SI should be obtained before thrombolysis is initiated within 3 to 6 hours. Once these advanced techniques are used, the therapeutic time window can be extended with acceptable safety. However, comprehensive informed consent is mandatory, especially when thrombolytic therapy is considered beyond established time windows. (Stroke. 2003;34:575-583.)

Key Words: computed tomography ■ magnetic resonance imaging, diffusion-weighted ■ magnetic resonance imaging, perfusion-weighted ■ magnetic resonance imaging, stroke ■ thrombolytic therapy ■ tissue plasminogen activator
documentation of an acute onset of focal neurological deficit with a baseline National Institutes of Health Stroke Scale (NIHSS) score, adherence to the general blood pressure guidelines, accounting for general rtPA contraindications, and exclusion of ICH by CT. These are the criteria by which rtPA was proven effective within 3 hours in the NINDS trial in 1995 and was approved by the Food and Drug Administration in 1996. We believe, however, that these are absolute minimum requirements that are not in keeping with the times and therefore should be extended by 1 or several of the following.

The European Cooperative Acute Stroke Study (ECASS) CT criteria define early signs of ischemic infarction that improve infarct detection and estimation of actual infarct size. The most common early infarct signs are a subtle gray matter and/or cortical hypodensity, loss of the insular ribbon, sulcal effacement due to early edema, and the hyperdense middle cerebral artery (MCA) sign. An early parenchymal hypodensity of >50% of the MCA territory is associated with an 85% chance of a fatal outcome. Treatment increased the chance of a good clinical outcome in patients with a small area of hypodensity (<33% of MCA territory), while rtPA in patients with a large area of hypodensity (>33% of MCA territory) caused no benefit but increased the risk for symptomatic ICH. Radiologists can be trained to recognize early infarct signs on CT. While several studies have shown the usefulness of early infarct signs in selecting patients before intravenous thrombolytic therapy, other studies demonstrated that physicians, including general radiologists and neuroradiologists, do not uniformly achieve a sufficient level of sensitivity for identifying CT contraindications for thrombolytic therapy. A post hoc analysis of the NINDS CT data (n=616) yielded a 31% sensitivity for early infarct signs, with a mild correlation with acute NIHSS score but no effect on either clinical outcome or ICH rate. However, it was not assessed whether outcome would have been better if rtPA had not been given to patients with early infarct signs of >33% of the MCA territory. Furthermore, these criteria apply more to patients in the 3- to 6-hour time window (ECASS I and II) because many CT scans are negative within the first 2 hours. Therefore, patients with early signs of infarction/demarcation >33% of the MCA territory should not be treated if no other information is available. Among stroke experts there is a consensus that patients with signs of profound ischemia with a strong hypodensity should not be given rtPA even within the 3-hour time window because of an excessive risk of ICH. Subtle early infarct signs might not definitely develop into infarction and therefore are partially reversible and, at least in the 3-hour time window, seem not to be correlated with efficacy of thrombolytic therapy or outcome. In conclusion, the established role of noncontrast CT with regard to therapeutic decision making agreed on by the NINDS and ECASS groups is the exclusion of ICH and the exclusion of patients with extensive demarcation of ischemic infarctions.

A new instrument for the improvement of CT rating is ASPECTS (Alberta Stroke Program Early CT Score). ASPECTS divides the MCA territory into 10 regions of interest as seen on 2 standardized axial CT slices (basal ganglia and lateral ventricles). The whole MCA territory is allotted 10 points (1 for each area), and a single point is subtracted for each of the defined regions if ischemic lesions are seen. Kappa statistics showed that the interobserver reliability of ASPECTS was higher than that of the one third MCA rule, although other preliminary data contradict these findings (W. Hacke, oral personal communication, 2002). The baseline ASPECTS value correlated inversely with the severity of stroke on the NIHSS ($r=-0.56$, $P<0.001$) and predicted functional outcome and symptomatic ICH ($P<0.001$; $P=0.012$). A sharp increase in dependence and death occurs with an ASPECTS value $>7$. While the ASPECTS instrument may be superior to the ECASS one third MCA rule, it is a refinement of that rule rather than a completely new development. Furthermore, it has not been validated for patients outside the 3-hour time window.

Another simple method to improve the diagnostic accuracy of noncontrast CT is the use of nonstandard, variable window width and level review settings. With standard viewing parameters, sensitivity and specificity for stroke detection were 57% and 100%, respectively; with soft window and variable settings, sensitivity significantly increased to 71% without loss of specificity ($P=0.03$).

**The 3- to 6-Hour Time Window**

All previous comments regarding CT are valid for the 3- to 6-hour time window as well. As stated previously, meta-analyses showed that thrombolytic therapy with rtPA reduces death and dependency with a number needed to treat of 17.5 (0 to 6 hours) or 25 (3 to 6 hours). Within 3 hours the number needed to treat was 7 or 8, depending on whether the analysis included data from the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial. Clinical criteria such as NIHSS scores above or below which rtPA should not be given did not prove to be helpful, although some authors advocate not administering intravenous rtPA in patients with NIHSS scores $\leq 3$ (good outcome in any case) or $>25$ (high risk of ICH and poor outcome).

**Doppler/Duplex Ultrasound**

The underlying rationale for the introduction and application of thrombolytic agents is the lysis of an obliterating thrombus and subsequent reestablishment of cerebral blood flow by cerebrovascular recanalization based on the penumbra concept. Therefore, beyond 3 hours after stroke symptom onset, proof of an occluded vessel by either Doppler ultrasound (DU), CT angiography (CTA), MR angiography (MRA), or digital subtraction angiography (DSA) should be established before rtPA is given even when the 3-hour cutoff has been chosen arbitrarily. On the other hand, there is no proof that patients without a vessel occlusion may not also benefit from thrombolytic therapy. It must be considered that an M2 branch occlusion may be below the detectability of Doppler, CTA, or MRA. A rapid workup of the patient who is a potential candidate for thrombolytic therapy is mandatory (“time is brain”).

The most widely available tool to noninvasively assess extracranial and intracranial vessel status is DU, which is a
suitable bedside tool not only to ascertain baseline vessel status but also to monitor the process or absence of recanalization, whether or not rtPA is applied. Early DU reports described that rapid recanalization was associated with a higher rate of clinical improvement and smaller infarcts at outcome.26 Clinical recovery from stroke correlated with the timing of arterial recanalization after thrombolysis, and complete recanalization was common in patients who had follow-up Rankin Scale scores of 0 to 1 (P=0.006).27 rtPA results in faster recanalization, a significantly higher recanalization rate (66% versus 15% in controls), and therefore a significantly smaller infarct volume and a significantly better clinical outcome at 3 months.28,29 Secondary ICH, which is associated with a worse clinical outcome, is significantly more frequent in patients with late rather than early recanalization.30 A pilot multicenter study evaluated color-coded duplex sonography in acute stroke patients before and after rtPA therapy.31 Recanalization of the occluded MCA after 2 and 24 hours was diagnosed in 50% and 78% of the patients treated with rtPA and in 0% and 8% in the control group. This is in agreement with data from MRI studies32 and illustrates that the largest effect of thrombolytic therapy is seen when rtPA is given to patients in whom a vessel occlusion has been established. Potential disadvantages of DU, however, are its examiner-dependent sensitivity, sensitivity for branch occlusions, and time-consuming nature as well as potential problems with uncooperative patients and lack of a transcranial insonation window.

CT/CTA/CTA Source Images

Direct comparison of CTA and DU suggests that the results from CTA compare favorably with ultrasound and that CTA can also reliably detect intracranial stenosis, emboli, and aneurysms of a moderate or larger size.33 Furthermore, it may easily be performed directly after noncontrast CT. In addition to the vessel status, CTA source images (CTA-SI) may render indirect information about the collateral circulation and also improve the contrast of perfused and malperfused brain areas, thus increasing the sensitivity for early ischemic changes not seen on noncontrast scans.34–36 Analysis of CTA-SI must be clearly differentiated from perfusion CT, in which, in analogy to perfusion-weighted MRI (PWI), a contrast bolus tracking method is applied, and hemodynamic parameters may be assessed.37 CTA-SI is a stronger predictor of clinical outcome than the initial NIHSS score and may predict final infarct volume and clinical outcome. Patients with recanalization do not experience infarct growth, whereas those without complete recanalization do.38 A comparison of CT/CTA/CTA-SI findings with diffusion-weighted MRI (DWI) and MRA reveals equal accuracy of CTA and MRA, close to equal accuracy of infarct volumes according to CTA-SI compared with DWI, and a predictive value of poor collaterals for infarct growth.39 Therefore, CT/CTA/CTA-SI may render information similar to that of the PWI/DWI mismatch concept.40

Dynamic Perfusion CT, Single-Photon Emission CT, Positron Emission Tomography

Dynamic perfusion CT during first pass of a contrast bolus can be used to construct functional maps of hemodynamic parameters (cerebral blood volume, cerebral blood flow, time to peak).41 Areas with reduced cerebral blood flow can be shown immediately after vessel occlusion with high contrast to areas with normal perfusion. Perfusion CT compared with single-photon emission CT (SPECT) and follow-up CT showed a good correspondence in 81% of the studied patients.37,42 In addition, the sensitivity of perfusion CT within 6 hours was substantially higher than that of noncontrast CT (100% versus 64%). Furthermore, perfusion CT criteria were established to differentiate irreversible from reversible ischemic damage within 6 hours after stroke onset.43 In some patients the ischemia was located outside the scanning level of perfusion CT and was therefore missed. This demonstrates the actual disadvantages of the method because with each bolus injection only 1 brain section (in multislice CT a maximum of two 1-cm slices) can be evaluated. Röther et al44 investigated the role of dynamic, single-slice CT perfusion imaging in the assessment of acute MCA stroke within the first 6 hours after symptom onset and before the start of treatment in a consecutive clinical series of 22 patients. Eighteen of their patients had perfusion deficits in the MCA territory and corresponding hypoattenuation on follow-up CT. Three patients with normal CT perfusion imaging findings showed lacunar infarctions or normal findings on follow-up CT. In 1 patient, CT perfusion imaging did not reveal a territorial deficit above the imaging slice. The overall sensitivity and specificity values of CT perfusion imaging for the detection of perfusion deficits in patients with proven territorial infarction (n=18) on follow-up CT were 95% and 100%, respectively.

While SPECT and especially positron emission tomography (PET) may render semiquantitative and quantitative hemodynamic data,45,46 these modalities are not widely available and thus are of academic interest but probably will not have any practical implications for the general stroke patient in the near future.

Stroke MRI

The advent of new MRI techniques such as PWI and DWI has revolutionized diagnostic imaging in stroke.47–50 DWI may delineate infarcted brain tissue within minutes, although there is growing evidence that in the very early stage of stroke there may be reversible DWI changes in up to 45% of patients experiencing recanalization after treatment with rtPA.51–54 However, these lesion reversals in most instances are only minor or partial and are quite frequently not permanent, and there are contradictory data as to whether a DWI/apparent diffusion coefficient threshold for irreversible ischemia exists.54–56 PWI defines the area of cerebral hypoperfusion. The absolute volume difference or ratio of PWI and DWI reveals the ischemic tissue at risk of irreversible infarction.57,58 Stroke MRI further allows a definitive diagnosis of ICH within the first hours of stroke and possibly a definitive diagnosis of subarachnoid hemorrhage as well.59,60 The susceptibility-weighted T2*-sequences detect hemorrhage due to a profound signal loss caused by paramagnetic effects of deoxyhemoglobin, even when only present in traces.61 Detection of old as well as new microbleeds and early hemorrhagic infarction by T2*-weighted imaging may allow
eventual recanalization may be substantially shorter with intra-arterial thrombolysis. The potential time delay to intra-arterial thrombolysis demands excellent logistics for neurointervention. Currently only few data support the combined use of intravenous and intra-arterial thrombolysis with rtPA; a phase II trial with 80 intravenous/intra-arterial patients compared with a historical control (NINDS) showed superior results of the combined approach. An initial workup either alone or in combination with DU, CT/CTA/CTA-SI, or stroke MRI is useful if arteriography is primarily applied to perform intra-arterial thrombolysis. As a purely diagnostic or screening means, invasive arteriography should not be performed because of the risk of potential complications.

The Unknown Time Window
Stroke physicians are frequently confronted with stroke patients in whom the exact time of symptom onset is not known, eg, those with deficit upon awakening, or cases in which the patient is not in a condition to give the required information because of aphasia or disorientation. At present, patients such as these are excluded from thrombolytic therapy even if a CT scan does not demonstrate any or only minor ischemic changes. Accordingly, thrombolysis as an effective therapy may be withheld from patients who might profit from rapid recanalization. Therefore, we suggest that patients presenting with symptoms of acute stroke of unknown onset time and without CT contraindications for rtPA should be investigated with stroke MRI or CT/CTA/CTA-SI and should be given thrombolytic therapy if a vessel occlusion and a substantial mismatch are present, perhaps even when only a perfusion deficit is present; a very cautiously phrased informed consent can be obtained by the patient or his/her closest relatives.

Vertebrobasilar Stroke
Vertebrobasilar distribution cerebral infarction has been of particular interest to centers experienced with local intra-arterial thrombolysis. Mortality of vertebrobasilar thromboembolism is high, with overall rates of approximately 70% to 80%. Successful recanalization, however, was associated with a survival rate of 55% to 75%, as opposed to 0% to 10% in persistent or untreated basilar artery occlusion. Two thirds of the survivors after recanalization had a favorable outcome; all survivors in the untreated group were moderately disabled. Other authors reported an overall mortality of 75% in 13 patients, although 10 of these had experienced nonrecanalization; nonrecanalization led to death in all patients (n=3). The authors concluded that recanalization of the vertebrobasilar system is necessary but not sufficient for effective treatment of vertebrobasilar occlusive disease. Grond et al reported a small case series of 12 consecutive patients in whom they investigated whether early intravenous thrombolysis could also effectively be applied in acute vertebrobasilar ischemic stroke. Patients with clinically diagnosed moderate to severe vertebrobasilar ischemic stroke with clearly determined symptom onset were treated with intravenous rtPA within 3 hours after symptom onset, following a protocol similar to that of the NINDS study. Of 12 patients in whom they investigated whether early intravenous thrombolysis could also effectively be applied in acute vertebrobasilar ischemic stroke. Patients with clinically diagnosed moderate to severe vertebrobasilar ischemic stroke with clearly determined symptom onset were treated with intravenous rtPA within 3 hours after symptom onset, following a protocol similar to that of the NINDS study. Of 12 patients in whom they investigated whether early intravenous thrombolysis could also effectively be applied in acute vertebrobasilar ischemic stroke. Patients with clinically diagnosed moderate to severe vertebrobasilar ischemic stroke with clearly determined symptom onset were treated with intravenous rtPA within 3 hours after symptom onset, following a protocol similar to that of the NINDS study. Of 12 patients in whom they investigated whether early intravenous thrombolysis could also effectively be applied in acute vertebrobasilar ischemic stroke. Patients with clinically diagnosed moderate to severe vertebrobasilar ischemic stroke with clearly determined symptom onset were treated with intravenous rtPA within 3 hours after symptom onset, following a protocol similar to that of the NINDS study. Of 12
patients, 10 had a favorable outcome after 3 months, defined as full independence (Barthel Index score of 100) or return to premorbid condition. Unfortunately, basilar artery occlusion was not demonstrated with any means such as DU, CTA, MRA, or DSA, and a single study with 12 patients does not suffice to give any recommendation for intravenous rtPA in these patients.

There are no data presently available that sufficiently document the utility of imaging techniques for decision making in vertebrobasilar stroke. CTA has been shown to be significantly superior to DU in demonstrating basilar artery occlusion. Stroke MRI has been used in our center as an exclusion criterion for neuroradiological intervention when large brain stem, bithalamic, and bilateral posterior cerebral artery infarctions could be demonstrated. However, sensitivity of DWI and especially PWI at the base of the skull is low because of bone-associated susceptibility artifacts. Neuroradiological intervention with intra-arterial thrombolysis to date is the only life-saving therapy that has demonstrated benefit with regard to mortality and outcome, albeit not in a randomized trial. However, sufficient data are available to justify intra-arterial thrombolytic therapy in the light of mortality and disability in these patients. The time window for thrombolysis in the posterior circulation has not been established but may be up to or even exceed 12 hours, although Fox et al suggest a time window of >10 hours to be associated with a poor prognosis.

**Informed Consent**

We are aware that our recommendations are not based on prospective randomized data and do not meet the criteria of an officially approved therapy. However, because there is already a substantial and still growing body of evidence in favor of the recommended procedures, these recommendations may be seen as an expert opinion and render the rationale for an individual therapeutic approach in an institutional protocol. The fact that an individual therapy based on advanced knowledge is offered, which does not meet the criteria of drug approval institutions and therefore may be associated with a higher risk of hazardous if not fatal side effects, must be stressed when informed consent is obtained. Conversely, it should be stated that the drawback of a later onset of therapy may be outweighed by a sophisticated diagnostic imaging procedure that informs the physician whether or not to treat. Patients and their relatives should be informed not only about the hazards of thrombolytic therapy within or outside the 3-hour time window but also about its potential benefit and thus the risk of not being treated.

**Conclusion**

In summary, we hypothesize that the optimal comprehensive diagnostic workup of acute stroke patients should not be limited to noncontrast CT as a means of excluding ICH, even if this is the present standard and absolute minimum procedure in the 3-hour time window. In our opinion, the minimum requirement is the utilization of alternative CT windows, early CT criteria, and perhaps ASPECTS. It can safely be assumed that a sophisticated differential indication for thrombolysis requires information about the presence or absence of a vessel occlusion whether by means of DU, CTA, or MRA in the 3 hours and should be obtained in the 3- to 6-hour time window. While optional but nevertheless optimal for patients within the 3-hour time window, advanced information such as clear demarcation of the irreversibly damaged infarct core and the ischemic but still viable and thus salvageable tissue at risk of infarction, as seen on DWI/PWI/ MRA or alternatively on CT/CTA/CTA-SI, should also be obtained before thrombolysis is initiated within 3 to 6 hours. There is no evidence available showing that patients without demonstration of an occlusion and with a PWI/DWI match (eg, lacunar stroke) might not profit from therapy. While this seems not likely to us, one might consider giving therapy in individual cases, since there is neither a relevant indication nor a contraindication. A mismatch without vessel occlusion is a hypothetical constellation but may be seen in distal MCA branch occlusions, where the occlusion may not be detected by rapid MRA sequences. Because of the low but increasing availability of stroke MRI as opposed to a wide distribution of modern CT scanners, a CT/CTA/CTA-SI protocol with or without DU is the alternate diagnostic modality of choice in these instances. However, it must be reiterated that randomized prospective and blinded trials to back these rationally well-based hypotheses are still lacking and should be the consequential next step (such as the EPITHET and DEFUSE trials currently being conducted in Australia and the United States, respectively). Therefore, we call for a large randomized controlled trial utilizing stroke MRI beyond the 3-hour time window. Further considerations are time constraints in the setting of thrombolysis, cost-effectiveness, and public health issues as well as availability of these advanced technologies. We believe, however, that the latter obstacles can be or already have been at least partially overcome.

We suggest that there are 4 distinct categories of patients: in 1 of these (category 2), the indication for thrombolysis in our opinion is moderate at best and not based on evidence but on questionable pathophysiological reasoning and thus may be a matter of individual debate; in 2 of these, thrombolytic therapy should be an urgent consideration also in the 3- to 6-hour time window and in infarctions of <33% of the MCA territory according to DWI (or CTA-SI). (1) We recommend no thrombolysis in patients with large infarctions >50% of the MCA territory according to DWI. (2) The indication for intravenous thrombolysis is a matter of debate but not performed in our center in (a) patients without PWI/DWI (or CT/CTA/CTA-SI) mismatch but with vessel occlusion; (b) patients with PWI/DWI (or CT/CTA/CTA-SI) mismatch but without (identifiable) vessel occlusion (eg, distal MCA branch); (c) patients without proof of vessel occlusion and without mismatch (eg, lacunar stroke); and (d) individual patients with PWI/DWI (or CT/CTA/CTA-SI) mismatch, vessel occlusion, and DWI (or CTA-SI) lesion volume between 33% and 50% of the MCA territory. (3) Intravenous and/or intra-arterial thrombolysis is indicated and essential in patients with MCA occlusions distal to the lenticulostriate branches and with presence of a PWI/DWI (or CT/CTA/ CTA-SI) mismatch. (4) Recanalization should be achieved by all means in patients with distal internal carotid artery or proximal MCA occlusions and presence of a PWI/DWI (or...
CT/CTA/CTA-SI mismatch. Alternatively to CTA or MRA, if the time constraints in the setting of thrombolytic therapy can be met, DU may be employed. Comprehensive informed consent is mandatory, especially when thrombolytic therapy is considered beyond established time windows.

Acknowledgments

This review presents the opinions and views of the authors and describes the decision-making process, ie, the therapeutic algorithm, utilized in our center. Drs Schellinger and Hacke have worked as consultants for Boehringer Ingelheim, and Dr Fiebach has worked as a consultant for Schering. None of the authors received funding or consultant fees for the preparation of this manuscript, and all the opinions are unbiased and based on the scientific work of our group and that of other experts in the field.

References


Imaging of cerebral ischemia has made tremendous progress within the last years. CTA provides evidence of cerebral artery occlusion, and CT perfusion imaging assesses perfusion deficits in acute stroke patients. Stroke MRI has taught all critics better that argued that it would not be possible to study a hemiplegic and aphasic stroke patient in a narrow and noisy bore hole. Fast gradients and improved acquisition routines made stroke MRI programs with DWI, PWI, MRA, fluid-attenuated inversion recovery (FLAIR), and blood-sensitive imaging to be standard for diagnostic workup in many specialized stroke centers around the world. The patterns for identifying the ideal candidate for thrombolysis are straightforward: a small infarct core identified by DWI and a large perfusion deficit on PWI in the presence of a vessel occlusion on MRA indicate the potential for a major opportunity for thrombolysis.1

Although this easy-to-apply paradigm is challenged by normalization of part of the diffusion lesion in patients treated with thrombolysis beyond the NINDS study.2 and although PWI is criticized for exaggerating the area of truly ischemic tissue, stroke MRI is simply the best technique available. Any alternative, be it PET, SPECT, or CT, is either not applicable in acute stroke patients or even less available than MRI. In the accompanying article, Schellinger and coauthors argue for overcoming the diagnostic standard of plain CT for stroke management and decision making. CT is currently the minimal diagnostic requirement and is less than can be expected in a specialized stroke center. Although CT exclusion of hemorrhage was the only imaging prerequisite in the NINDS study,3 many stroke neurologists feel more confident with tPA treatment after the identification of some kind of mismatch. Mismatch does not necessarily imply DWI/PWI mismatch but can consist of a CT with minor early ischemic signs but a MCA main stem occlusion diagnosed with CTA or Doppler ultrasound. One might argue that a neurological deficit with 15 points on the NIHSS score and a normal CT fulfills the criterion of a “mismatch”; however, this is exactly the opportunity advanced imaging provides: to prevent a strategically located lacunar infarct or a brain stem infarction or a stroke mimic from being treated with tPA if there is no target tissue. Advanced stroke imaging is still optional but optimal in the 3-hour window.

The limitation to a specific time window lacks concrete pathophysiological reasoning, and there is evidence for persisting salvageable tissue even at 48 hours after stroke onset.4 Meta-analyses of intravenous tPA given within the 3- to 6-hour time window show efficacy, but the benefit is smaller and the risk of bleeding is higher.5 It is obvious that with increasing time from stroke onset the volume of tissue at risk shrinks, the likelihood of hemorrhage increases, and the therapeutic benefit lessens.6 Advanced stroke imaging offers the chance to focus thrombolytic treatment on the ideal candidate with a relevant penumbral zone in the extended time window. Recent studies have shown that a relevant
volume of salvageable tissue is present in >80% of stroke patients in the 3- to 6-hour time frame.\textsuperscript{1,7,8} Randomized controlled trials are running that even extend the window for thrombolysis up to 9 hours on the basis of stroke MRI (Desmoteplase in Acute Ischemic Stroke [DIAS]).

Schellinger and colleagues suggest thrombolytic therapy under conditions that are considered an exclusion criterion according to existing treatment guidelines: thrombolysis in patients with unknown time window is not consensus. However, many stroke neurologists share the experience of successful thrombolysis in these patients and offer tPA in the presence of a large DWI/PWI mismatch after informed consent is obtained. The presence of a mismatch is time dependent, and the presence of a large mismatch volume argues for a short delay since stroke onset and a realistic chance of benefit. However, “chronic mismatch” may persist in the case of sufficient collateral pathways, and caution must be taken.

Schellinger and coauthors give constructive recommendations for the use of tPA within an extended time window. Although randomized controlled trials are still awaited, recent open trials support thrombolysis in the 3- to 6-hour window, especially in the presence of a DWI/PWI mismatch.\textsuperscript{1} Thrombolysis in patients without mismatch seems questionable (recommendation 2). The pathophysiological reasoning is based on a small series of patients with diffusion normalization after treatment with intra-arterial thrombolysis.\textsuperscript{2} Data on the rate of apparent diffusion coefficient normalization in intravenously treated patients have not yet been published. Other unpublished data (J. Röther, MD, 2002; n=50) show that the rate of diffusion normalization in tPA-treated patients treated intravenously in the 6-hour time window is approximately 20% and the tissue volume that normalizes is low (5 to 29 mL). Therefore, it seems that the potential benefit in patients without mismatch is limited.

In conclusion, many stroke centers apply advanced imaging techniques—mainly stroke MRI and advanced multimodal CT—to obtain a higher level of certainty and safety for the indication of thrombolytic therapy. One major goal is the extension of the rigid time window in order to offer tPA to a broader stroke population. Whether patient selection with DWI/PWI in an extended time window results in better outcomes must be shown in future studies (EPITHET trial).

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