Acute Stroke Imaging for Thrombolytic Therapy – An Update

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Abstract

More than ten years after its approval intravenous thrombolysis with rtPA still is the only approved therapy for acute ischemic stroke. In this review we aim to give an up-to-date overview of acute stroke imaging within and outside of approved indications for thrombolysis. We discuss the potential applications of modern CT techniques such as CT angiography and perfusion CT as well as stroke MRI for the selection-based treatment of acute ischemic stroke. Recent publications regarding diagnostic strength as well as new randomized trials and larger prospective but open studies are reviewed and discussed. Finally we present a suggestion for the selection of patients for thrombolysis within and beyond the 3-hour time window in the form of an institutional algorithm prioritizing according to present evidence and pathophysiological reasoning. Copyright © 2007 S. Karger AG, Basel

Introduction

Intravenous thrombolysis using recombinant tissue plasminogen activator (rtPA) is still the only approved therapy for acute ischemic stroke (AIS). While non-contrast CT to exclude hemorrhage is still the gold standard and according to approval guidelines the only needed imaging modality to select patients for thrombolysis, extensive research is carried out to refine imaging techniques in the acute setting. The goal in this effort is to securely diagnose AIS and at the same time to identify those patients most likely to benefit from therapy while excluding those patients with a high risk for complications. In the following article, we provide an overview on advances in acute stroke imaging for thrombolysis.

Intravenous Thrombolysis Based on Advanced CT Imaging

Noncontrast CT imaging is currently the most widely used diagnostic tool for stroke imaging [1] mainly due to its close to 100% high sensitivity for intracranial hemorrhage (ICH), the most important differential diagnosis to ischemic stroke [2]. Modern CT scanners of the 3rd, 4th or even 5th generation (volume scanners) are available in many centers even in smaller community hospitals, where

they are mostly used for extracranial scanning. Acute stroke is not only treated at specialized academic medical centers; indeed, the majority of patients present first in local general hospitals that have no MRI facilities [3].

Noncontrast CT and Early Ischemic Changes

Standard treatment within the 3-hour time window is still mostly done according to the protocol of the NINDS trial based on exclusion of hemorrhage using noncontrast CT [4]. The use of 'early ischemic changes' (EIC) on CT to further select patients for treatment is a field of controversy. While the NINDS trial did not exclude patients based on EIC, the ECASS trials formulated the so called 'one third MCA rule' [5]. Patients with hypoattenuation in more than one third of the middle cerebral artery (MCA) territory were excluded from both ECASS trials. For ECASS I, a post-hoc analysis demonstrated that patients with hypoattenuation larger than one third of the MCA territory did not benefit from treatment [6]. One has to keep in mind though that this analysis was only possible because 52 patients with large EIC were wrongly included into the trial and, therefore, the analysis was made on a very special population of patients which should not have been in the trial in the first place. This also highlights the main problem with EIC. They are very hard to read and show a poor sensitivity and interrater agreement [7]. The lack of clear definitions for EIC and the heterogeneity of the pathophysiological background of different subtypes have added to the uncertainty surrounding these signs. Improvements of readings have been achieved with a more formalized approach using the Alberta Stroke Program Early CT Score (ASPECTS) [8, 9]. While the ASPECTS may be superior to the ECASS one third rule, it is rather a refinement of that rule than a completely new development. It divides the MCA territory into ten regions of interest as seen on two standardized axial CT slices (basal ganglia and lateral ventricles). The whole MCA territory is allotted 10 points (one for each area) and a single point is subtracted for each of the defined regions if ischemic lesions are seen. However, regardless of using the one third MCA rule or ASPECTS a treatment effect modification by baseline evaluation of EIC could not be detected within the 3-hour time window NINDS trial dataset [10, 11]. In contrast, several studies show such a predictive value of EIC for populations beyond 3 h. This was demonstrated by a post-hoc analysis of the ECASS II trial – a population that was mainly treated beyond 3 h as well as an analysis of the PROACT-2 dataset [12, 13]. For ECASS II, a low ASPECTS was predictive for risk after thrombolysis in patients be-

yond 3 h but not in patients treated within the 3-hour time window. A treatment modification by baseline ASPECTS was not observed in either group [12]. In the PROACT-2 population, an ASPECTS of >7 predicted a benefit from intra-arterial thrombolysis. In conclusion, to date there is no evidence to exclude patients within the 3-hour time window from thrombolysis based on EIC. However, a large area of manifest hypodensity within 3 h should raise doubts about the accuracy of the reported time of stroke onset. Beyond the 3 h, one might be careful treating patients with an apparent hypoattenuation exceeding one third of the MCA territory or an ASPECTS of ≤ 7 . Another simple method to improve the diagnostic accuracy of noncontrast CT is the use of nonstandard, variable window width and level review settings. In one study, sensitivity and specificity for stroke detection were 57 and 100% with standard viewing parameters, with narrow window and variable settings sensitivity significantly increased to 71% without loss of specificity ($p = 0.03$) [14].

CT Angiography and CTA Source Images

Today, CT angiography (CTA) using spiral CT is a widely available tool to evaluate the circle of Willis. In AIS patients, this technique can provide accurate information on stenoses or occlusions in the basal arteries of the brain [15, 16]. The method is noninvasive, safe and independent of the grade of experience of the investigator. In experimental studies [17] as well as larger series of stroke patients, there were no immediate adverse reactions after administration of the intravenous nonionic iodinated contrast material [16]. Newer generations of CT scanners allow for lower contrast doses. A recent study addressed the frequency of contrast-induced nephropathy in acute stroke imaging [18]. Of 526 patients receiving CTA, DSA or both, none developed acute renal failure needing dialysis and only 7 patients (3.3%) showed signs of mild radio-contrast nephropathy. Therefore, acute CTA alone or combined with DSA appears to be safe in acute stroke patients. If urgent CTA is critical for acute stroke decision making, this study supports proceeding without knowledge of baseline creatinine level [18].

In addition to the assessment of a major vessel occlusion, CTA has the potential to deliver information about the quality of the collateral circulation. In patients with good leptomeningeal collaterals, contrast enhancement in arterial branches beyond the occlusion occurs. This degree of enhancement can be taken as an estimate of the collateral blood flow [15, 19]. Analysis of CTA-SI must be clearly differentiated from perfusion CT (PCT), where in

analogy to perfusion MRI a contrast bolus tracking method is applied and hemodynamic parameters may be assessed [20]. CTA-SI analysis is a stronger predictor of clinical outcome than the initial NIHSS score and may predict final infarct volume and clinical outcome. Schramm et al. [21] investigated whether CTA-SI allow to detect ischemic brain lesions in patients with AIS, whether their sensitivity is comparable to that of DWI, whether the hypoperfused brain area seen on CTA-SI correlates with the final infarct and whether the qualitatively assessed collateral status does reflect the risk of infarct growth. Similar to the perfusion imaging (PI)/DWI mismatch concept, a poor collateral status predicted a significantly worse clinical outcome without recanalization. CTA-SI may indeed provide information similar to that of the PI-DWI mismatch concept. The volume of the affected brain area that has inadequate blood supply can be estimated by the difference between the CTA-SI lesion volumes and the brain area supplied by the occluded artery, taking the qualitative assessment of the collateral status into account. The patients with poor collaterals seem to represent those that may have a PI-DWI mismatch in analogy to stroke MRI and the patients with good collaterals those patients without tissue at risk.

Dynamic PCT

PCT allows to generate functional maps of cerebral blood volume, cerebral blood flow (CBF) or time-to-peak (TTP) enhancement calculated from a contrast bolus time curve in analogy to PI [20, 22–24]. However, calculated thresholds for cerebral blood volume, TTP and CBF differ between various scanners, perfusion postprocessing techniques and other variables. Nevertheless, pathological findings on PCT are predictive of lesions at follow-up [25]. Also CTA-SI and DWI as well as PI and PCT seem to compare favorably [26]. In some patients, ischemia is located outside the scanning level of PCT, which at present covers 2 cm at the most with one assessment. Some authors therefore recommend 2 PCT acquisitions with a gap of 1 cm to obtain 5 cm brain coverage. This may be limited by cumulative contrast and radiation exposure on the other hand. New and already available developments in CT technology, including dynamic scanning with multisection data acquisition (multislice CT), may further increase the value of this technique and provide information about the three-dimensional extent of cerebral ischemia. Wintermark et al. [27] also compared stroke MRI and PCT/CTA in 42 acute stroke patients in the 3- to 9-hour time window, 14 of whom were treated with thrombolysis. Agreement between PCT/CTA and

MRI was excellent regarding infarct size and the penumbra/infarct ratio. Agreement for treatment decisions based on algorithms was also excellent. Only one patient would have been treated based on MRI, and not CT. Therefore, if stroke MRI is not available, advanced CT imaging appears to be a viable alternative imaging option rendering comparable results [26, 27]. Currently, there are no larger studies examining the use of advanced CT techniques for selection of patients for thrombolysis. Present studies such as the DIAS-2 study allow the use of advanced CT techniques beside the main MRI arm. Thus, these studies will not only yield information about the use of these CT techniques but also allow to compare them to modern multiparametric MRI approaches.

Intravenous Thrombolysis Based on Advanced MRI

Although Nobel prizes seem to be awarded to developers of imaging techniques (1979, Hounsfield for CT; 2003, Lauterbur and Mansfield for MRI), the last but most important step for a new technology is the establishment in clinical practice. Despite the work that followed by Sir Peter Mansfield [28, 29] and other groups, the first clinical MRI system was not available until 1984 and the first paramagnetic MRI contrast agent until 1987. Within the past 20 years, several advances in computer technology and software development have been realized, and these changes have continuously improved the accessibility and quality of MRI. The earliest scans – T₂-weighted, T₁-weighted and PD-weighted sequence without contrast – literally took hours to complete. Today, multiparametric protocols can assess within 15 min the most complex pathophysiological processes, which allows for a dramatic shift in the evaluation and treatment of neurological illness. As the clinical discipline of neurology has evolved from a diagnostic to a therapeutic specialty, MRI has been and is being transformed into a clinical tool that impacts on neurology at the bedside. It is exciting that with an increasing number of clinical therapeutic trials being designed, MRI may not only function as a diagnostic tool but also have prognostic strength and thus, serve as a selection tool and a surrogate endpoint for the development of new therapies [30].

Pathophysiological Concepts Transferred to MRI in AIS

The target for most therapeutic interventions for focal ischemia should be ischemic tissue that can respond to treatment and is not irreversibly injured (i.e. the ischemic

penumbra). Until recently, only PET and SPECT imaging could approximately define ischemia and penumbra thresholds. However, application of these methods in the clinical setting of acute stroke is not practical or feasible. Newer imaging techniques such as novel MR pulse sequences, perfusion techniques and other improvements of imaging soft- and hardware have provided the opportunity to improve the diagnostic yield.

Two MRI techniques that have received much attention in the past 15 years are diffusion-weighted sequences and PI [31–34]. In the classical model, the DWI lesion represents the irreversibly damaged core of the infarct. Now that more patients have been evaluated with stroke MRI and at early time points, partial reversal of the initial DWI lesion has been reported. These findings suggest that the DWI lesion might be included in the therapeutic target, not as the definite infarct core [35–38]. However, DWI lesion reversal is associated with ultra-early and permanent reperfusion and this per se is a far stronger predictor of clinical and imaging outcome [39]. In most instances and especially in later time windows, the DWI lesion may adequately reflect permanently damaged brain tissue.

The idea that quantitative PI is required for stroke assessment is derived from concepts of ischemic thresholds and ischemic penumbra, the premise being that if CBF could be accurately quantified then the tissue could be characterized as normal, reversibly ischemic, or irreversibly damaged. Unfortunately, a variety of factors noted above make this unlikely to be the case in human patients. Firstly, the duration as well as extent of ischemia must be known, and such information is not available from a single study acquired at the time of presentation. Secondly, human stroke typically involves both gray and white matter, whereas threshold data apply primarily to gray matter. Thirdly, while some human strokes such as those caused by thromboembolism in atrial fibrillation consist of a solitary MCA occlusion, many human strokes are multifocal or are caused by partial occlusions and in these cases a complex topological relationship is likely to occur between ‘core’ and ‘penumbra’ including variations between cortical laminae. Fourthly, mathematical approaches to account for bolus delay and dispersion are complex [40]. Finally, it is now recognized that delayed cell death occurs as a result of ischemia (apoptosis) and also that recurrent sublethal ischemia can make the brain less sensitive to subsequent ischemic events (ischemic conditioning) [41].

Most authors, however, agree that time-based parameters such as mean transit time or TTP give the best prog-

nostic information [42, 43] for patients with AIS. Further PI research is aimed at differentiating oligemia from critical ischemia [38] with the goal of better guiding clinical management. It has been shown that a time thresholding on mean transit time or TTP maps may increase accuracy. Neumann-Haefelin et al. [44] found a threshold of 4 s on TTP maps to indicate moderately severe and beyond 6 s to indicate severe ischemia. Sobesky et al. [45] compared PI to H_2O^{15} PET imaging and also showed that a threshold of 4 s gains the best sensitivity and specificity for critical, i.e. penumbral, hypoperfusion [46]. Thus, while hypoperfusion remains a key pathophysiological mechanism in stroke, it is no longer clear that absolute quantification of CBF at any one moment in time is sufficient or even necessary for predicting tissue outcome. More practically, the ‘ischemic penumbra’ may be operationally defined as those brain regions which are at risk of infarction but remain salvageable [47].

The volume difference of DWI and PI – also termed PI/DWI mismatch – gives an approximate measure of this tissue at risk of infarction [48]. While its nonquantitative approach suffers from in part inaccurate PI measurements and the fact that DWI abnormalities may reverse [38], they serve their purpose of easy clinical application. In fact, most experts agree that from a practical standpoint this simple model of PI/DWI-mismatch is sufficiently accurate in most acute stroke patients, and furthermore stroke MRI findings are consistent with our understanding of the pathophysiology of acute ischemia [1, 43]. Applying the mismatch concept may identify the individual time window for the patient and thus allow therapeutic decision making based on an individual vascular and hemodynamic situation, rather than the elapsed time. Additional MR findings not captured by CT, such as early blood brain barrier disruption [49] and old microbleeds [50, 51] may predict a poor outcome after thrombolysis and, therefore, can be used to improve patient selection although this has been contradicted [52]. It is established that microbleeds are associated with a higher risk of hemorrhagic and ischemic stroke in general [53]; however, whether the one time risk of ICH after treatment with rt-PA is increased is at present unknown [54]. Preliminary data of more than 800 patients [55] indicate that microbleeds in fact do not increase the risk for symptomatic ICH (sICH) after thrombolysis. Therefore, the presence of microbleeds currently should not influence our treatment practice, but in the face of doubt may be used as an exclusion criterion in reperfusion studies to increase safety.

Comprehensively Diagnosing Stroke with MRI

The supposed lack of feasibility and practicality of MR as a diagnostic tool in hyperacutely ill patients has been consistently disproven. Many centers have demonstrated that logistical obstacles can be overcome [56–59]. Despite this, substantial doubts remain regarding the feasibility and practicality as well as the validity of stroke MRI in the clinical setting [60, 61]. This criticism is mainly based on a supposed lack of studies that assess sensitivity and specificity of these new imaging methods in a randomized, blinded and controlled fashion. Also, the overextensive use of the term ‘imaging gold standard’ has added to the controversy, as there remains no such thing as an imaging gold standard for AIS due to the current lack of correlations of any neuroimaging method with neuropathological findings [62]. Therefore, as a quasi-gold standard the diagnosis of ischemic stroke in most studies is established at follow-up with proof of a lesion on either CT or conventional MR images consistent with a clinical syndrome and a comprehensive diagnostic workup.

Several studies addressed the diagnostic power of stroke MRI for ischemic as well as hemorrhagic stroke. Fiebach et al. [63] prospectively evaluated a total of 50 patients with ischemic stroke and 4 patients with transient ischemic attacks. To avoid any bias in favor of the neuroimaging strategy, the patients were randomized to the sequence of imaging modalities (either stroke MRI or CT first followed by the other). Five stroke experts and 4 residents independently judged stroke signs and lesion size on the images. The sensitivity and interrater variability of infarct detection by the experts was significantly better when based on DWI. Also, the assessment of lesion extent was more homogeneous than based on CT. The differences between the 2 modalities were stronger in the residents’ ratings. In the recently published HEME-ER study, the diagnostic superiority of MRI over CT in the differential diagnosis of suspected acute stroke has again been established [64]. In a sample of 356 patients (217 of whom with the final diagnosis of acute stroke) CT and MRI had comparable specificity (98% CT vs. 96% MRI) for AIS, but sensitivity was significantly better for MRI (16% CT vs. 83% MRI).

With regard to hemorrhage, Fiebach et al. [65] conducted a multicenter trial with 62 prospectively acquired patients with ICH and with ischemic stroke, who were assessed within 6 h after symptom onset using DWI, T₂-weighted imaging and T₂*-weighted imaging. Baseline CT, follow-up imaging and clinical course were used to establish the correct diagnosis of ICH and ischemic stroke, respectively. Three raters blindly and indepen-

dently rated all scans. All ischemic strokes and ICH were correctly identified by all 3 raters, also specificity, positive and negative predictive values, and accuracy were 100%. Kidwell et al. [66] compared the accuracy of MRI and CT in a prospective, blinded multicenter design in 200 patients within 6 h after symptom onset. For the diagnosis of any hemorrhage, MRI was positive in 71 patients with CT positive in 29 ($p < 0.001$). For the diagnosis of acute hemorrhage, MRI and CT were equivalent (96% concordance). Acute hemorrhage was diagnosed in 25 patients on both MRI and CT. In 4 other patients, acute hemorrhage was present on MRI but not on the corresponding CT. In 49 patients, chronic hemorrhage, most often microbleeds, was visualized on MRI but not on CT. These studies demonstrate that MRI is as good as CT to detect ICH in the acute setting.

Guiding Therapy with Stroke MRI

Despite its potential, only 1–2% of all stroke patients receive rt-PA [67]. Among the major problems are that relatively few candidates present within the time window, and meet the clinical criteria. Educating the general public to regard stroke as a treatable emergency and training emergency caregivers in the use of thrombolysis can decrease these problems but demands a continuous effort. Healthcare institutions should be made aware of the potential in long-term cost savings, once stroke management is optimized and thrombolytic therapy is more widely available. Stroke physicians are frequently confronted with stroke patients who awaken with a deficit [68] or are unable to provide the required information due to aphasia or disorientation. At present, such patients are excluded from thrombolytic therapy, even if a CT scan is normal or has only minor ischemic changes. In these patients, who might profit from rapid recanalization, thrombolysis is often withheld.

Several investigators found a significant correlation of DWI and PI changes with follow-up imaging as well as with neurological outcome [69–74]. Some authors concluded that different infarct patterns can be identified by means of DWI and PI in hyperacute stroke, which may allow a more rational selection of therapeutic strategies based on the presence or absence of tissue at risk [1, 38, 47, 75]. Only recently has this concept been proven in The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study [76]. DEFUSE was a 7 center trial, which recruited 74 patients treated with rtPA within 3–6 h after symptom onset based on CT findings. An MRI was obtained immediately prior to and after rtPA. Early reperfusion was associated with signifi-

cantly better chance for a favorable clinical response to thrombolysis in patients with a PI/DWI mismatch. Patients without a mismatch did not benefit from early reperfusion. Large infarctions already seen on baseline DWI experienced fatal sICH upon reperfusion, while small (lacunar) infarcts did reasonably well with or without a mismatch [76]. One concern with using MRI as a screening tool has been, that it takes longer than noncontrast CT and thus delays treatment. A recent study by Kang et al. [77] showed that within the 3-hour time window, MRI is associated with a longer door-to-needle time and onset to treatment time but that this delay does not lead to a less favorable outcome. Furthermore, recent studies on MRI-based thrombolysis in the extended time window beyond 3 h show that time to treatment was neither a predictor for outcome nor for safety within such selected patients [58, 59]. MRI is presently used in most of the major stroke centers worldwide for the management of acute stroke beyond the NINDS time criteria, with thrombolysis rates ranging from 10 to 25% of all stroke patients in these centers. In due time, MRI may become not only the most powerful but also the most widely and potentially uniformly used tool to guide therapy based on individual pathophysiology rather than a surrogate parameter such as elapsed time.

Prospective Studies

After the earlier smaller studies, recently two large observational studies using stroke MRI in an extended time window in clinical practice as well as two randomized phase II trials – the DIAS and the DEDAS trial – have been published. Thomalla et al. [58] compared outcome and symptomatic bleeding complications of intravenous rtPA within 6 h of symptom onset in MRI-selected patients with acute MCA infarction with the pooled data of the large stroke rtPA trials. Favorable outcome was more frequent in MRI-selected rtPA patients compared with pooled placebo and pooled rtPA patients. Interestingly, the rate of sICH in MRI-selected rtPA patients was lower than in the pooled rtPA group and comparable to the pooled placebo group. Our group compared in a single center study patients who were treated with rtPA based on CT findings within 3 h with patients treated based on MRI within and beyond 3 h [59]. Clinical outcome and occurrence of sICH were prospectively assessed in 382 consecutive patients. Patients were divided into 3 groups: (1) CT based, <3 h (209 patients); (2) MRI based, <3 h (103 patients), and (3) MRI based, >3 h (70 patients). The rate of independent outcomes in groups 1–3 was 47.8, 50.5 and 55.7%, respectively. Mortality was trendwise reduced,

Fig. 1. Suggested algorithm.

and sICH were significantly reduced in the MRI-based groups. MRI-selected patients overall had a significantly lower risk for sICH and mortality. In multivariate analysis, only age and treatment based on MRI were significant predictors of sICH, whereas for independent outcome and mortality age, NIHSS score and sICH were predictive. Time to treatment proved to be irrelevant for all outcomes in univariate and multivariate analyses.

Two parallel phase II trials (DIAS, DEDAS) with a 3- to 9-hour time window using another thrombolytic drug (desmoteplase) have recently been completed. In DIAS, reperfusion rates up to 71.4% were observed with desmoteplase (125 µg/kg) compared with 19.2% with placebo [78]. Favorable 90-day clinical outcome was found in 22.2% of placebo-treated patients and between 13.3% (62.5 µg/kg; $p = 0.757$) and 60.0% (125 µg/kg; $p = 0.009$) of desmoteplase-treated patients. Early reperfusion correlated favorably with clinical outcome ($p = 0.0028$). Favorable outcome occurred in 52.5% of patients experiencing reperfusion versus 24.6% of patients without reperfusion. The DEDAS study yielded confirmatory results. Interestingly, in both studies imaging parameters paralleled the clinical outcome, proving that the MRI parameters function as adequate surrogate parameters [79]. Also, as shown in the other studies using an MRI-based selection process within 3–9 h it does not matter when the therapy is given. If a mismatch was present, time from symptom onset was not a treatment effect-modifying factor. The follow-up phase III study DIAS-2 was completed recently and another trial, the DIAS-C (confirmatory)-trial, is already in preparation.

Suggested Treatment Algorithm

The following treatment algorithm (fig. 1) is based on an institutional protocol and not primarily on international guidelines. However, a recent publication presents algorithms from several of the leading groups of MRI-based management of stroke and these algorithms are fairly consistent [80]. Whenever possible, explicit informed consent should be obtained from the patient or the next of kin, if available, should be informed about the individual treatment character of these recommendations. It acknowledges the fact that at present approval of thrombolysis is based on CT diagnosis within the 3-hour time window and, therefore, states this procedure as the highest priority. Generating evidence by participating in randomized trials is second priority. The open use of stroke MRI as pictured in this review is priority 3. Whether

there should be an upper time limit remains a matter of controversy. However, many centers choose 6 h (ECASS trials) or 9 h (DIAS/DEDAS) as a time limit, albeit again it must be stressed that this is an off-label therapy. Patients with unknown time window are included if strict MRI criteria are met [68, 81]. A fourth priority is based on advanced stroke CT criteria (CT, CT angiography, perfusion CT). As described above, this technique has been far less validated in stroke studies and not at all in treatment studies. Nevertheless, preliminary data and common sense dictate that stroke CT can be used in a similar fashion as stroke MRI; however, maybe with less diagnostic strength. Finally, based on the combined analysis [82], if neither a study, stroke MRI or stroke CT is available, there is sufficient evidence for expanding the time window to 4.5 h with noncontrast CT only.

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