Neuroimaging of Cerebral Ischemia and Infarction

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Summary: The imaging workup for patients with suspected acute ischemic stroke has advanced significantly over the past few years. Evaluation is no longer limited to noncontrast computed tomography, but now frequently also includes vascular and perfusion imaging. Although acute stroke imaging has made significant progress in the last few decades with the development of multimodal approaches, there are still many unanswered questions regarding their appropriate use in the setting of daily patient care. It is important for all physicians taking care of stroke patients to be familiar with current multimodal computed tomography and magnetic resonance imaging techniques, including their strengths, limitations, and their role in guiding therapy. **Key Words:** Stroke, brain infarction, CT, MRI, perfusion, reperfusion therapies.

INTRODUCTION

In the last few years, substantial advances have been made in the treatment of acute cerebral ischemia. In particular, thrombolytic agents have provided a means to improve the clinical outcome of acute ischemic stroke patients and to reduce the proportion of patients with disability and death. Other promising reperfusion therapies, including mechanical embolectomy, are currently under investigation. With the development of physiologic imaging modalities, such as perfusion-computed tomography (PCT) and perfusion-weighted magnetic resonance imaging (PWI), and with the advent of fast and reliable noninvasive angiographic techniques, a completely new neuroimaging perspective of ischemic stroke has been introduced. Advanced imaging plays a growing role not only in the diagnosis of stroke but also in the selection of patients for acute therapies. This review will briefly discuss the individual components of multimodal magnetic resonance (MR) and multimodal CT imaging, review the role of these imaging modalities in the characterization of ischemic penumbra and in the selection of patients for reperfusion therapies and, finally, discuss the future steps needed in this field.

FROM STRUCTURAL TO FUNCTIONAL MULTIMODAL STROKE IMAGING

In the past, acute stroke imaging consisted of simple structural imaging modalities. As such, noncontrast CT (NCT) was typically used to rule out hemorrhage and other stroke mimics and to potentially detect the presence of early, subtle acute ischemic signs. With the development of multislice CT, new MR sequences, and fast and reliable post-processing software, imaging has now the capability to evaluate acute stroke as a dynamic and evolving process—in contrast to the previous static all-or-none approach. In particular, the neuroimaging community has made important advances in operationally defining ischemic "penumbra" with CT and MRI techniques currently available in the acute stroke setting.

Penumbral imaging

Prior to the introduction of an effective therapy capable of limiting the size of an acute cerebral infarct, the ischemic penumbra was more a theoretical rather than a practical matter. Following an arterial occlusion, a core of brain tissue dies rapidly. Surrounding this infarct core is an area of brain that is hypoperfused, but still viable. This area at risk, but comprising potentially salvageable tissue, is called the ischemic penumbra [1–3]. The evolution of the infarct core and penumbra is a dynamic process that depends mainly on the collateral flow, but also on the timing and extent of reperfusion of the ischemic tissue. If the vascular occlusion remains, the infarct core will likely grow and progressively replace

the penumbra. If prompt recanalization is achieved, either spontaneous or thrombolysis related, the penumbra may be rescued from infarction [4].

With the approval of intravenous recombinant tissue plasminogen activator (rt-PA) for the treatment of acute ischemic stroke, the concept of the penumbra has gained increasing importance as an indicator of the volume of brain tissue that is potentially salvageable after a successful treatment [5]. Indeed, at the present time, intravenous rt-PA is routinely accepted as the only proven treatment for acute ischemic stroke in the first 3–4.5 h after symptom onset [6]. However, very few patients are admitted in this narrow time window and, as a result, less than 10% of acute ischemic stroke patients are treated [7]. It has been hypothesized, however, that intravenous rt-PA or other reperfusion therapies could be safely administered in an extended time window in selected patients with a sufficient amount of salvageable penumbra [8, 9], which would allow a much larger percentage of stroke patients to be safely treated. This concept emphasizes the urgent need for advanced imaging techniques capable of delineating the ischemic penumbra in the acute stroke setting [10]. During the last decade, several operational definitions of ischemic penumbra have been proposed using MRI and, increasingly, CT. Furthermore, some studies have suggested a favorable clinical outcome with thrombolytic therapies administered to patients selected on the basis of penumbral imaging in an extended time window [11].

Vascular imaging

Vascular imaging, combined with penumbral imaging, provides another fundamental piece of information in the workup of acute ischemic stroke patients and in the assessment of the response to reperfusion therapies. Patients should be differentiated based on the amount of ischemic penumbra as well as on the initial angiographic findings since the location and the extent of vascular obstruction have important prognostic value in predicting response to thrombolytics [12, 13]. For instance, patients with a "carotid-T" occlusion, proximal middle cerebral artery (MCA) occlusion, tandem lesions or significant thrombus burden might respond poorly to intravenous thrombolytics, and therefore may be appropriate candidates for subsequent intra-arterial or mechanical thrombolysis [14–16].

Multimodal stroke imaging

By combining parenchymal, penumbral, and vascular imaging in one single study, multimodal CT and MR provide a comprehensive hyperacute stroke imaging evaluation. Both approaches can 1) exclude intracranial hemorrhage (ICH) and other mimics of ischemic stroke, 2) provide reliable information about the location and

extent of ischemia, 3) identify the existence and extent of potentially salvageable brain, and 4) identify the site of vascular occlusion and degree of collateral flow. Multimodal CT and MRI have been shown to be fast, reliable, and effective in improving stroke detection and characterization in the emergency setting [17], and to have the potential to select patients that may benefit from reperfusion therapy [11].

ACUTE STROKE MRI PROTOCOL

A typical multimodal stroke MRI protocol consists of T2/fluid-attenuated inversion recovery (FLAIR)-, T2*-, diffusion (DWI)- and perfusion (PWI)-weighted imaging and MR angiography (MRA) [17]. This protocol can be performed in <15–30 min.

Location and extent of the acute ischemia: DWI

DWI provides an image signal that is dependent on the molecular motion of water [18]. Cerebral ischemia leads to a disruption of energy metabolism, with disruption with failure of the Na+/K+ ionic pump causing cytotoxic edema [1]. Intracellular water flow leads to a reduced extracellular volume, whereby water mobility is relatively facilitated and, therefore, to a net reduction of water diffusion [4, 18]. This phenomenon can be detected as a hyperintense signal on DWI scans within minutes of vessel occlusion (FIG. 1) [4, 18]. In addition, an apparent diffusion coefficient map can be constructed to quantify the extent of restricted diffusion.

The main advantage of MRI over CT is that DWI is the most sensitive method to date for the depiction of ischemia in the hyperacute stage [19, 20]. It should be noted, however, that DWI lesions can be at least partially reversible in the very early phase of ischemia and, as such, the initial DWI abnormality does not necessarily reflect the infarct core [21]. An additional advantage of DWI is its ability to distinguish acute from chronic ischemia, thereby allowing new lesions to be identified in patients even when these are near or within areas of prior ischemic injury. DWI can also visualize small lesions not evident on CT scans, particularly in the posterior fossa; the location and pattern of these lesions often provide insight into the underlying stroke mechanism.

Exclusion of other stroke mimics and study of the brain parenchyma: T2-/FLAIR images

Cerebral ischemia usually becomes visible within the first 3–8 h after stroke onset on T2-weighted and FLAIR images [22–24]. A recent study has shown that, in acute stroke patients with a DWI-positive lesion, a normal FLAIR image suggests a time window of less than 3 h with >90% specificity and positive predictive value.
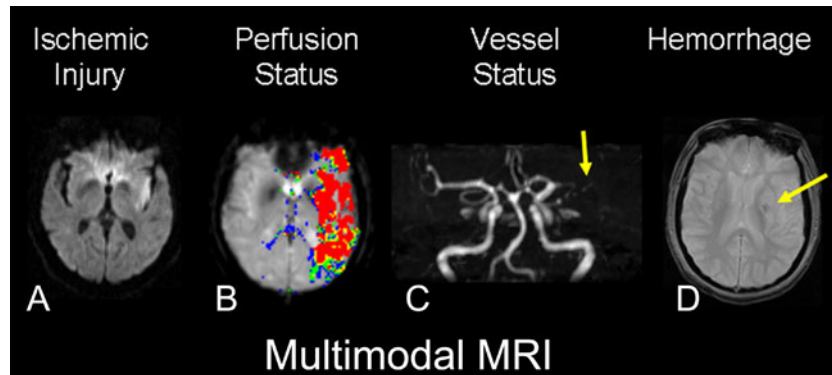
FIG. 1. Example of multimodal MRI in acute stroke: (A) DWI showing hyperintense ischemic region in the left insula. (B) Tmax perfusion MRI demonstrating left MCA perfusion deficit. (C) Intracranial MRA demonstrating left MCA occlusion (arrow). (D) gradient echo MRI emonstrating small region of hemorrhagic transformation (arrow). MRI = Magnetic resonance imaging; DWI = diffusion-weighted MR; MCA = middle cerebral artery. With kind permission from Kidwell and Wintermark [62, figure 1, page 22]. Copyright, Springer Science and Business Media. (High resolution version of this image is available in the electronic supplementary material.)

Thereby, a mismatch between DWI-positive and DWI-negative FLAIR images may be a reliable approach for the identification of unknown onset stroke patients who are likely to benefit from thrombolysis [23]. FLAIR images are also highly sensitive in detecting other lesions, including subarachnoid hemorrhage and acute cerebral venous sinus thrombosis [25–27].

Exclusion of intracranial hemorrhage: T2*-weighted images

Although CT is the standard method used to rule out ICH, gradient-recalled echo and other T2* sequences are equally—if not more—sensitive for the detection of acute ICH, even by relatively inexperienced readers (FIG. 1) [28, 29].

Furthermore, small hemosiderin deposits not apparent on CT scans can be detected by T2*-weighted images [29]. These chronic microbleeds are an indicator of a hemorrhage-prone vasculopathy and are associated with an increased risk of spontaneous ICH. The relationship between chronic microbleeds and post-thrombolysis-related hemorrhage is still being debated [20, 21]. In the BRASIL study [30], the odds ratio for symptomatic hemorrhage following the intravenous administration of rt-PA in patients with microbleeds *versus* without was 2.23 (95% confidence interval, 0.67–6.97). The authors concluded that any increased risk of thrombolytic therapy in the setting of microbleeds is likely to be small and unlikely to exceed the benefits of treatment. Due to the very small number of patients with multiple microbleeds, no reliable conclusions could be drawn regarding the risk in this subgroup.

Finally, due to the high concentration of deoxyhemoglobin in the acute thrombus, T2*-weighted images are able to detect intraluminal clots as linear or dot-shaped low-signal areas of magnetic susceptibility [24].

Location and extent of the arterial occlusion: MR angiography (MRA)

3-Dimensional time-of-flight MRA is the standard technique for the examination of intracranial vessels. This sequence depicts vascular flow by repeatedly applying saturation pulses to a volume of tissue. Stationary protons in the excited plane become saturated by the repeated pulses, whereas inflowing blood protons are not and, therefore, produce a relatively increased signal intensity [24, 31].

Contrast enhanced-MRA is the technique of choice for the study of the extracranial arteries. It relies on the injection of gadolinium to reduce the T1 relaxation time of tissue and to generate contrast between the intravascular lumen and surrounding tissues [32]. Unlike time-of-flight MRA, vascular contrast is relatively independent of flow dynamics and, therefore, artifacts are substantially reduced.

MRA is employed for the detection of the location of the vascular occlusion and/or stenosis in both the intracranial and extracranial vasculature (FIG. 1) [24, 32].

Location and extent of the hypoperfused area: PWI

PWI provides a measurement of cerebral perfusion by tracking the bolus passage of a paramagnetic MRI contrast agent administered intravascularly [33]. Using a dynamic contrast-enhanced technique, the temporal passage of gadolinium is tracked in repeated contiguous slices throughout all of the brain volume using T2*. The tissue signal change caused by the susceptibility effect of gadolinium is used to create a hemodynamic time-to-signal intensity curve and then to generate a set of semiquantitative perfusion maps [34]. These include maps of relative cerebral blood flow (CBF), mean transit time (MTT), cerebral blood volume (CBV), and time-to-peak (TTP; including Tmax, which is the TTP of the residue function) measures. CBV reflects the blood volume per unit of brain, MTT designates the average

time required by the contrast bolus to cross the capillary network, CBF relates to the volume of blood flowing per brain mass during a time interval of 1 min, and TTP and Tmax measure the time to peak of the contrast agent within the vessel. The relationship between CBF and CBV is expressed by the equation $CBF = CBV/MTT$ [35, 36].

The main advantage of MR PWI over PCT is the whole brain perfusion coverage of the former that allows the detection of small but potentially clinically relevant hypoperfusion areas. The main disadvantage of PWI is that the measures are semiquantiative rather than absolute.

ACUTE STROKE CT PROTOCOL

Multimodal CT stroke protocol

A typical multimodal stroke CT protocol consists of NCT, PCT, and CT angiography (CTA). This protocol can be performed in <10 min.

Exclusion of other stroke mimics and assessment of early CT signs of ischemia: NCT

Due to its wide availability, speed, and patient tolerance, NCT has traditionally been the first-line imaging modality for the evaluation of acute ischemic stroke. NCT is mainly used to rule-out intracranial hemorrhage.

In some cases, NCT can identify signs of early ischemia in hyperacute stroke [37–39]. These include the insular ribbon sign, obscuration of the lentiform nucleus, and the presence of hyperdense vessels (FIGS. 2

FIG. 2. NCT scan of the brain in a 71-year-old male obtained 4 h after the onset of symptoms shows an obscuration of the left lentiform nucleus. NCT = Noncontrast computed tomography. (High resolution version of this image is available in the electronic supplementary material.)

and 3). The first two signs allude to the partial disappearance or loss of definition of the gray–white matter interface. The latter, caused by the presence of an acute hyperdense thrombus in a vessel (often the middle cerebral artery), 1does not represent a sign of infarction but, rather, is a hallmark of an acute thrombo-embolic event. Although those early signs can be helpful in confirming the location and diagnosis of ischemia, their detection is difficult and depends on the experience of the reader. Hence, infarct detection with NCT in the first 3 h after onset is a challenge, with sensitivity values as low as 25% in comparison with DWI-MR [40]. It should be noted that the relationship between early ischemic changes visible on the CT images and adverse outcomes after rt-PA treatment is not straightforward and that the presence of early infarct signs on the NCT scan should not be considered a contraindication to thrombolytic treatment [41, 42].

Unlike these subtle hyperacute ischemic changes, obvious hypoattenuation is highly specific for tissue infarct, [43] and its extent is predictive of the risk of hemorrhagic transformation [44], clinical outcome, and final infarct volume. Frank hypoattenuation on the CT scan, particularly when it involves more than one-third of the MCA territory, has been used in most clinical trials as an exclusion criterion for thrombolysis due to the potential increased risk for hemorrhagic transformation [45].

Despite its advantages, NCT provides solely structural—and not physiologic—information, and it cannot reliably differentiate between irreversibly damaged brain tissue and penumbral tissue.

Location and extent of the arterial occlusion: CTA

CTA allows a fast and detailed evaluation of the intra- and extracranial vasculature in one single contrast injection [46, 47]. Its speed and high spatial resolution make it a powerful tool by which to evaluate the vasculature in acute stroke patients and support its inclusion in an acute stroke imaging protocol [46, 47]. The information obtained from the arterial imaging may be used to guide therapy. Several studies have shown an association between occlusion site, recanalization success rate, and clinical outcome [14–16]. Currently available multidetector CT scanners may have the ability to dynamically assess the collateral flow [48]. This additional piece of information might play a role in the therapeutic workup.

Location and extent of the hypoperfused area: PCT

PCT imaging relies on the speed of modern helical CT scanners that can sequentially trace the entry and washout of a bolus of standard iodinated contrast agent injected into a peripheral vein [36]. Analysis of the signal density during the passage of the contrast agent provides information on brain capillary perfusion [35]. The linear
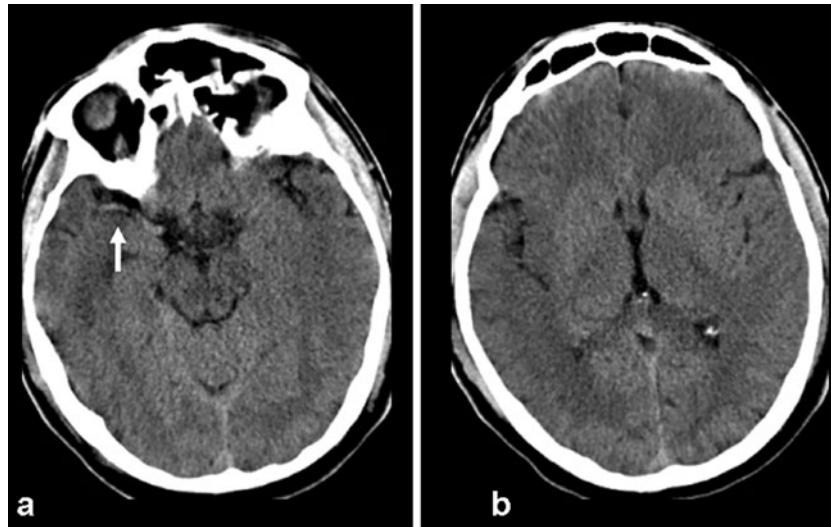
FIG. 3. NCT scan of the brain in a 66-year-old male obtained 5 h after the onset of symptoms shows hyperdense right MCA (a) (arrow) and insular cortical ribbon loss signs (b). (High resolution version of this image is available in the electronic supplementary material.)

relationship between the concentration of the contrast agent and CT tissue density provides quantitative assessments of cerebral perfusion, which is a significant advantage of PCT over PWI. As with MRI, PCT evaluation of brain perfusion consists of 3 main sets of values and parametric maps: CBV, MTT, CBF (FIG. 4).

The main limitation of PCT is its inability to image the whole brain, as conventional scanners are limited to a 2- to 4–cm section of brain tissue per contrast bolus. Progressive introduction of the new volumetric CT scanners, offering whole brain coverage, is likely to overcome this limitation in the near future [48].

Of note, a recent study has demonstrated that not only does PCT provide an assessment of hemodynamic status, but that this assessment in turn improves diagnostic accuracy for ischemia over that achieved with NCT alone or with combined NCT and CTA, even when read by inexperienced radiologists [17].

NEUROIMAGING FOR THE DIFFERENTIATION OF INFARCT CORE AND PENUMBRA

Differentiation of the infarct core and ischemic penumbra relies on the concept of cerebral vascular autoregulation [35, 49, 50]. Vascular autoregulation consists of complex neurobiochemical mechanisms that guarantee the stability of regional CBF despite changes in the local neuronal metabolic activity or in the local arterial perfusion pressure. It notably allows for a pre- and postcapillary dilatation in response to a decreased perfusion pressure in order to maintain a constant CBF. In the penumbra, where autoregulation is intact or mildly jeopardized, MTT is prolonged; however, the CBV is

maintained or increased due to this compensatory vasodilatation. In tissue proceeding to infarction, CBF is low and autoregulation is impaired, leading to low CBV values with a loss of ability to maintain vasodilatory compensation [35, 49].

MRI

Initial MRI approaches to characterizing the ischemic core and penumbra were based on the simplified assumption that the DWI abnormality reflects the irreversibly damaged infarct core, whereas the PWI abnormality reflects the overall area of hypoperfusion [51]. The volumetric difference between these images, i.e, the PWI/DWI-mismatch, was thought to represent the ischemic penumbra (FIG. 1). Since these initial studies, however, it has been shown that this model does not take into consideration that DWI lesions do not necessarily turn into infarction and that the PWI abnormalities may also represent areas of benign oligemia that are not at risk [21, 52]. Moreover, to date, threshold approaches to differentiating core and penumbra have also not been shown to have high levels of accuracy. A study of 10 different MR perfusion methods using different postprocessing revealed differences in hypoperfused tissue volumes depending on the parameter used to calculate them [53]. In current clinical practice, however, Tmax and MTT are the parameters most often used. Efforts are underway to identify more accurate multivariate MRI models that incorporate information on a voxel level from both perfusion and apparent diffusion coefficient maps. These approaches have the potential to have greater sensitivity and specificity in predicting the tissue core and penumbra in the hyperacute window [54].
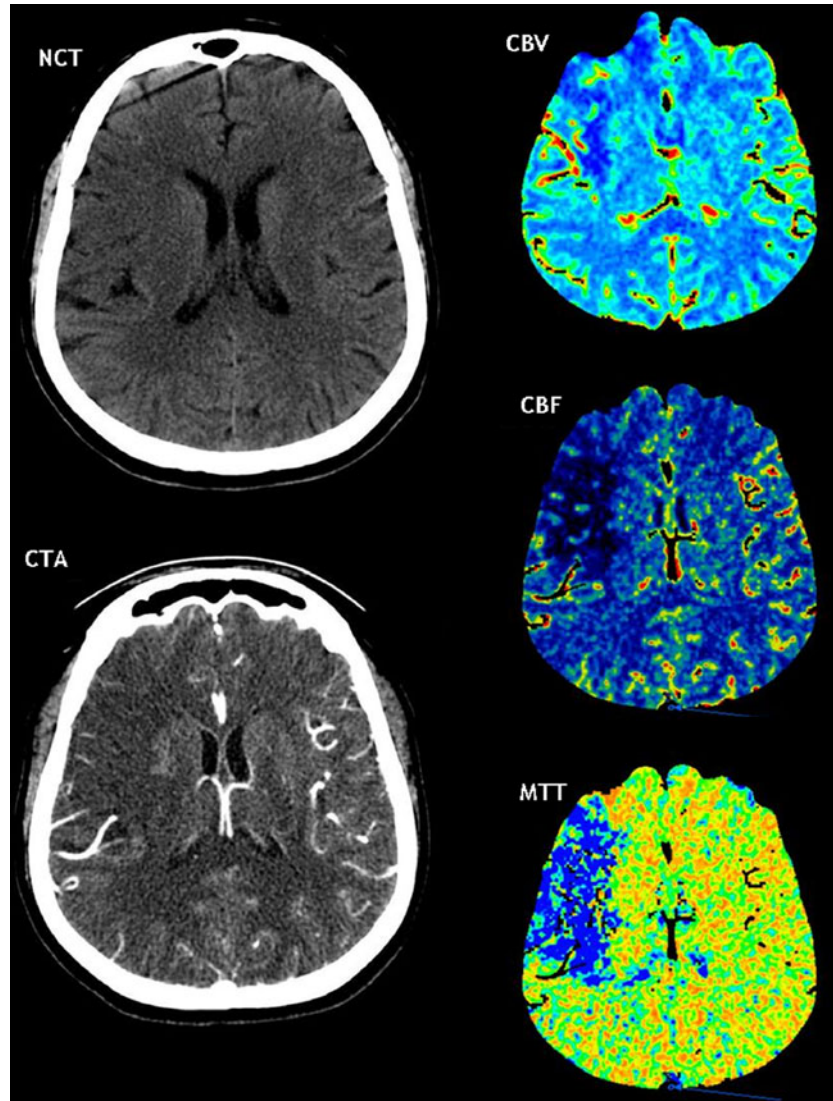
FIG. 4. Multimodal CT imaging in a 63-year-old female patient with acute stroke obtained 4 h after symptom onset. NCT scan shows subtle loss of the gray–white matter interface in the right parietal lobe. CTA demonstrates a paucity of MCA distal branches in the affected brain area; no proximal MCA occlusion was found. PCT parametric maps show a nearly complete match between the MTT and CBV parametric maps. The patient was not treated with rt-PA. CTA = CT angiography; PCT = perfusion-CT; MTT = mean transit time; CBV = cerebral blood volume; rt-PA = recombinant tissue plasminogen activator. (High resolution version of this image is available in the electronic supplementary material.)

PCT

By combining quantitative MTT and CBV results, PCT has the capacity to reliably identify the reversible ischemic penumbra and the irreversible infarct core in acute stroke patients [55]. In the infarct core, MTT is prolonged and CBV is low, whereas in the penumbra, MTT is prolonged but CBV is high due to vasodilatory compensation. Quantitatively, the parameter that most accurately describes the tissue at risk of infarction is the relative MTT, with an optimal threshold of 145% [55]. The parameter that most accurately describes the infarct core on admission is the absolute CBV, with an optimal threshold of 2.0 ml/100 g [54]. The PCT correlate for the infarct core and ischemic penumbra has been validated by prospective studies and been shown to compare to the PWI/DWI MR mismatch [50, 56].

NEUROIMAGING FOR THE SELECTION OF PATIENTS FOR THROMBOLYTIC THERAPY: CURRENT EVIDENCE AND FUTURE PERSPECTIVES

There is a growing body of data suggesting that multimodal imaging can be used for selecting patients for acute reperfusion therapies. The DIAS and DEDAS trials randomized patients within a 3- to 9-h time window after stroke setting and with a DWI/PWI mismatch of at least 20% either to placebo or to escalating doses of a novel thrombolytic drug, desmoteplase [8, 9]. Those patients who received a placebo or an ineffective dosage showed a lower recanalization rate and an unfavorable outcome. In comparison, those patients who achieved early vessel

recanalization and reperfusion of penumbral tissue, showed a significant clinical benefit, with 60% of the patients from the most effective dose tier having an excellent clinical outcome [8].

In the DIAS 2 study [57], patients were enrolled based on a mismatch diagnosed either by MR or by PCT. Unfortunately, this study did not show any benefit in clinical outcome in either of the treatment groups, contrasting sharply with the previous findings with desmoteplase in the DIAS and DEDAS trials.

The DEFUSE study showed that baseline MRI findings can be used to identify groups of patients who are more likely to benefit from thrombolytic therapy and, potentially, other forms of reperfusion therapy [11]. Patients with a baseline mismatch between PWI and DWI of at least 20% and a reduction in abnormal perfusion volume of at least 10 mL had a better clinical outcome. Data from this study suggested that a mismatch ratio (PWI volume − DWI volume/DWI volume) of 2.6 provided the highest sensitivity and specificity for identifying patients in whom reperfusion was associated with a favorable response. However, no benefit could be expected if early recanalization of the occluded vessel failed, even in the presence of a large mismatch [58].

The most recent data supporting the use of penumbral selection comes from the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), which was a randomized, controlled multicenter trial of IV rt-PA *versus* placebo 3–6 h from onset [59]. All patients underwent pretreatment MRI, but findings were not used to determine eligibility. While the primary outcome, infarct growth measured by the geometric mean, was not statistically significant, a secondary outcome of growth, namely, the median growth ratio, was significant in favor of attenuated growth in the rt-PA arm in mismatch patients. The investigators also found that reperfusion was significantly correlated with growth attenuation and improved outcomes. Unfortunately, they also found there were insufficient numbers of non-mismatch patients to compare groups.

Although acute stroke imaging has made significant progress in the last few decades with the development of multimodal approaches, there are still many unanswered questions regarding their appropriate use in the daily patient care. The role and utility of multimodal imaging of intravenously administered rt-PA candidates within 4.5 h is unclear—further clinical trial data are needed to weigh the risks and benefits of this approach. Clinical trials of acute reperfusion therapies in an extended time window have shown mixed results. New trials should overcome the limitations of these previous studies. Two main barriers that need to be solved are the lack of standardization and the validation of analytic approaches, especially for the penumbra imaging [60]. The various

trials published to date used different perfusion models, different sequence parameters, and even different thresholds for defining core and penumbra [61]. After the key step of standardization, additional large multicenter trials are needed to validate these techniques to definitely demonstrate that advanced imaging selection for reperfusion therapies improves clinical outcome. Approaches to vascular imaging should also be standardized and this information incorporated into protocols to optimize trial design, including the outcome assessment of both recanalization and reperfusion [12, 61].

CONCLUSIONS

Multimodal MRI and CT techniques provide a comprehensive assessment of the size, location, and severity of cerebral ischemia, hemodynamic compromise, and vessel occlusion. The combined information can be used to determine the presence and extent of infarct core and penumbra. Clinical trials to date suggest that this information may be used to select optimal candidates for reperfusion therapies. However, future studies are needed to provide a valid standardized penumbra model that can be widely employed by the neuroimaging community and to demonstrate that multimodal imaging selection improves outcomes.

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