Neuroimaging for acute ischemic stroke: current challenges

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Abstract: Over the last decade, neuroimaging methods have been refined to improve clinical decisions regarding acute stroke treatment. Computed tomography and magnetic resonance imaging are routinely used to rule out intracerebral haemorrhage or other contraindications of thrombolysis, to detect stroke mimics and to estimate the time of stroke onset. With the availability of fast and advanced imaging methods, there is a growing interest in expanding their application for the prediction of success and risks of specific therapies. The mismatch concept, which has long been controversial, has now experienced a breakthrough due to further development and standardisation of imaging parameters, and a separation of different, clinically relevant mismatch patterns. In this review, we will highlight existing neuroimaging modalities for acute stroke. To interpret neuroimaging results, knowledge about the clinical situation is essential. Furthermore, the factors of time since stroke onset and collateral blood supply need to be incorporated into existing imaging-based therapeutic strategies.

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Abstract

Over the last decades, neuroimaging methods have been refined to improve clinical decisions regarding acute stroke treatment. Computed tomography (CT) and magnetic resonance imaging (MRI) are routinely used to rule out intracerebral hemorrhage or other contraindications of thrombolysis, to detect stroke mimics and to estimate the time of stroke onset. With the availability of fast and advanced imaging methods, there is a growing interest in expanding their application for the prediction of success and risks of specific therapies. The mismatch concept, which has long been controversial, has now experienced a breakthrough due to further development and standardization of imaging parameters and separation of different, clinically relevant mismatch patterns. In this review, we will highlight existing neuroimaging modalities for acute stroke. To interpret neuroimaging results, knowledge about the clinical situation is essential. Furthermore, the factors of time since stroke onset and collateral blood supply need to be incorporated into existing imaging-based therapeutic strategies.

CT in acute stroke

A plain non-contrast-CT scan is sufficient to perform thrombolysis in acute stroke patients if all contraindications can be excluded (1995). Since the European Cooperative Acute Stroke Study (ECASS) III trial, intravenous thrombolysis with recombinant tissue-type plasminogen activator (rtPA) has been approved for up to 4.5 hours from symptom onset in Europe and appears to be safe within this time window (Hacke et al., 2009; Ahmed et al., 2013). Despite this extended therapeutic window, rtPA can only be given to a small fraction of stroke patients (de Los Rios la Rosa et al., 2012). This is because the potential benefit of treatment has to be balanced against the risk of hemorrhage in the individual patient. There is an inverse relationship between time from stroke onset and successful recanalization with thrombolysis (Hacke et al., 2004).

Non-contrast brain CT is fast and easily available, helping to minimize delays within the hospital ("door-to-needle times"), and therefore still the preferred primary imaging modality in many stroke centers (Ferrari et al., 2013). In addition to non-contrast CT, CT angiography (CTA) and/or CT perfusion (CTP) imaging are increasingly available for stroke patients (Wintermark et al., 2006). They allow visualizing extra- and intracranial arteries, including plaque characteristics as well as collateral flow (Delgado Almandoz et al., 2010; McVerry et al., 2012). Earlier drawbacks of a significantly increased radiation dose have been overcome by improved hardware and post-processing capabilities in new generation CT scanners (Hochberg and Young, 2012). CT perfusion allows imaging of brain tissue perfusion through sequential CT acquisitions following an intravenous bolus of an iodinated contrast agent. The following parameters are derived in most CTP applications: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and Time to peak

(TTP) (Konstas et al., 2009). After deconvolution of a reference arterial input function, MTT is derived. CBV is the area under the time-contrast-enhancement curve, TTP the time to peak contrast enhancement, and CBF is calculated as CBF = CBV/MTT (Axel, 1983).

MRI in acute stroke

MRI is increasingly available as an alternative imaging modality in acute stroke and allows several non-contrast image acquisition modalities as well as MR angiography (MRA) and MR-based perfusion-weighted imaging (MRI-PWI). From the latter and similar to CTP, the parameters CBF, CBV and MTT can be derived (Barbier et al., 2001; Calamante et al., 2002; Hochberg and Young, 2012). In addition to bolus-tracking techniques that rely on the application of an MRI contrast agent, arterial spin labeling MRI measures perfusion by non-invasively, magnetically labeling endogenous water protons (Detre et al., 1994; Hendrikse et al., 2012). The method is gaining access to clinical MRI protocols and has the unique potential to selectively analyze blood supply from a single, magnetically labeled vessel ("vessel encoded imaging") or with blood flow of a pre-defined velocity ("velocity selective imaging"), which is not feasible with bolus-tracking CTP or MRI-PWI methods (Wong et al., 2006; Wong, 2007). The MRI sequence parameter that has revolutionized stroke imaging in the 90s was the non-contrast application diffusion weighted imaging (DWI) (Latchaw et al., 2009). DWI can readily depict even small ischemic lesions within the first minutes/hours of stroke onset and has proven to be more sensitive in ischemic lesion detection than CT (Barber et al., 1999). MRI is at least as good as CT with respect to the detection of acute intracranial hemorrhage (Chalela et al., 2007). Stroke mimics such as seizures, migraine or encephalopathy are typically not discerned on a non-contrast CT (Forster et al., 2012). Although the complication rate

of thrombolysis in stroke mimics is low, patients would receive a potentially harmful therapy unnecessarily. In patients presenting with ambiguous clinical symptoms raising doubt about an ischemic cause, MRI would be the preferred imaging modality.

Another challenge for the physician is stroke occurring during the night ("wake up stroke") or in other situations when the onset is unknown. These patients were previously excluded from thrombolysis. Using DWI and fluid-attenuated inversion recovery (FLAIR) MRI, it is now possible to estimate the onset of stroke into < or > 6 hours earlier (Thomalla et al., 2011). Patients with a wake-up stroke, who have a DWI positive lesion that is not demarcated on FLAIR are very likely to be within a time window where thrombolysis can still be performed. Both sequences can be acquired within 5-10 minutes. Since stroke occurs during the night in about 25% of patients, this concept may significantly increase the eligibility of acute stroke patients for thrombolysis.

Despite these advantages of MRI, the applicability to acute stroke patients is often limited due to the required head restrain, difficulties in patient monitoring, and exclusion of patients with pacemakers or claustrophobia.

The target mismatch

Initially described by Astrup in 1983, the penumbra is tissue at risk of infarction due to a reduction in blood flow, hypoxia and loss of functionality that has however not yet caused irreversible failure of energy metabolism and necrosis (Astrup et al., 1981; Paciaroni et al., 2009). The concept of "mismatch" is an attempt to define this area by imaging with the goal to search for tissue that is hypoperfused but still salvageable by recanalization even beyond the approved treatment time window or to select patients

for endovascular treatment. It was initially used in the context of a MRI-PWI and DWI mismatch for MRI assessment in acute stroke patients (Farr and Wegener, 2010). The infarct core is the area where MRI-PWI and DWI lesions are overlapping; indicating that hypoperfusion in these areas has already progressed to infarction. With time and with persistence of the vascular occlusion, the core is expected to grow. After results from smaller studies indicated that the PWI-DWI mismatch may indeed help to select patients for safe thrombolysis at treatment times > 4.5h (Warach, 2002; Schellinger et al., 2003; Thomalla et al., 2007), the concept was introduced into larger clinical trials, where a patient was grouped as having a mismatch when the lesion on MRI-PWI was 20% larger than the DWI lesion (Donnan et al., 2009). (Fiebach and Schellinger, 2009; Schabitz, 2009). These trials (DEFUSE, EPITHET, DIAS-2), although showing a favorable response to thrombolysis with mismatch, could not prove that patient selection for thrombolysis based on the mismatch was beneficial (Albers et al., 2006; Davis et al., 2008; Donnan et al., 2009; Hacke et al., 2009). The results were probably influenced by differences in post-processing of the perfusion maps (Dani et al., 2011). A separate, retrospective analysis of the DEFUSE data showed that the correlation between MRI-PWI lesion and final infarct size depends on the thresholds applied to the calculation of the PWI maps (Olivot et al., 2009). However, another re-analysis of the pooled DEFUSE-EPITHET data revealed that not only technical aspects might have contributed to the disappointing results regarding the interpretation of the mismatch: in patients between 3 and 6 hours of symptom onset with a mismatch, but with a “malignant” profile, defined as large (>80ml) DWI and large (>85ml with Tmax > 8sec) MRI-PWI lesion, recanalization caused even worse outcomes, due to the increased occurrence of parenchymal hemorrhage (Mlynash et al., 2011). These findings suggest that recanalization strategies should be pursued with caution in

patients presenting at later (>3h) time points with a MRI-defined malignant profile. Exclusion of patients with a malignant profile and dichotomizing into patients with/without a “target mismatch” demonstrated that indeed patients with a target mismatch respond better to recanalization therapies, as in the prospective, randomized DEFUSE2 trial (Lansberg et al., 2012). Currently, several trials are ongoing testing the target mismatch as a selection criterion to extend the thrombolysis time window to up to 9 hours or test endovascular recanalization (Fisher and Albers, 2013). CT has also been used to provide a mismatch, whereby MTT/TTP and CBV/CBF maps are overlaid in analogy to MRI-PWI and DWI, with MTT and CBV probably yielding the best prediction for infarct growth (Wintermark et al., 2006). In this model, the core is the area of decreased CBV embedded into the larger area of prolonged MTT. Although the correlation to the MRI-defined mismatch is fairly good, the approach suffers from the fact that it can assess contrast-based perfusion parameters only, and does not measure an independent tissue parameter such as DWI to estimate the core.

What is the underlying vascular physiology of a target mismatch versus a malignant profile in similar vascular occlusions? A proficient collateral vascular network might be present in some patients. Such collaterals might maintain perfusion and slow down growth of the ischemic core. It is conceivable that differences in collateral supply or in tissue resistance to ischemia might contribute to the observed imaging patterns (Shuaib et al., 2011). If different growth dynamics are to be expected, the influence of time should be incorporated into existing models of infarct growth. Recanalization may still lead to clinical improvement when achieved within the first 3 hours of symptom onset in patients with a malignant profile and/or poor collaterals, but may be beneficial even at much later time points in a target mismatch patient with

good collaterals (for an example of a patient with a target mismatch see figure 1). It is very likely that advanced neuroimaging including CTP and MRI-PWI will facilitate the introduction of new and better treatments for acute stroke patients in the near future.

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Figure 1: Patient with target mismatch without reperfusion

Legend: 83 year old patient presenting 3 hours after the onset of aphasia and right sided, sensorimotor paralysis. The CTP including MTT and CBV maps and the DWI-MRI, acquired 1.5 hours later, show a target mismatch in a MCA-M1 occlusion. Despite timely start of thrombolysis, recanalization could not be achieved. The FLAIR MRI acquired 3 weeks later demonstrates that with persisting M1-occlusion, the infarct has grown into the full area of prolonged TTP on the initial CTP map.