

# NEUROIMAGING OF ACUTE ISCHAEMIC STROKE: CURRENT CHALLENGES

\*Susanne Wegener

*Department of Neurology, University Hospital Zurich, Zurich, Switzerland*

*\*Correspondence to Susanne.Wegener@usz.ch*

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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.

**Keywords:** Stroke, cerebral blood flow, mismatch, magnetic resonance imaging (MRI), computed tomography (CT), neuroimaging.

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## COMPUTED TOMOGRAPHY (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.<sup>1</sup> Since the European Cooperative Acute Stroke Study (ECASS) III trial, intravenous thrombolysis with recombinant tissue-type plasminogen activator (rtPA) has been approved in Europe for up to 4.5 hours from symptom onset, and appears to be safe within this time frame.<sup>2,3</sup> Despite this extended therapeutic window, rtPA can only be given to a small fraction of stroke patients.<sup>4</sup> This is because the potential benefit of treatment has to be balanced against the risk of haemorrhage in the individual patient. There is an inverse relationship between time from stroke onset and successful recanalisation with thrombolysis.<sup>5</sup>

Non-contrast brain CT is fast and easily available, helping to minimise delays within the hospital ('door-

to-needle times'), and therefore still the preferred primary imaging modality in many stroke centres.<sup>6</sup> In addition to non-contrast CT, CT angiography (CTA) and/or CT perfusion (CTP) imaging are increasingly available for stroke patients.<sup>7</sup> They allow visualisation of extra and intra-cranial arteries, including plaque characteristics as well as collateral flow.<sup>8,9</sup> Earlier drawbacks of a significantly increased radiation dose have been overcome by improved hardware and post-processing capabilities in new-generation CT scanners.<sup>10</sup> CTP 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).<sup>11</sup> After deconvolution of a reference arterial input function, MTT is derived. CBV is the area under the time contrast-enhancement curve, the TTP contrast enhancement, and CBF is calculated as  $CBF=CBV/MTT$ .<sup>12</sup>

## MAGNETIC RESONANCE IMAGING (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 magnetic resonance (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.<sup>10,13,14</sup> In addition to bolus-tracking techniques that rely on the application of an MRI contrast agent, arterial spin labelling MRI measures perfusion by non-invasively, magnetically labelling endogenous water protons.<sup>15,16</sup> The method is gaining access to clinical MRI protocols and has the unique potential to selectively analyse blood supply from a single, magnetically labelled 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.<sup>17,18</sup>

The MRI sequence parameter which revolutionised stroke imaging in the 1990s was the non-contrast application diffusion-weighted imaging (DWI).<sup>19</sup> DWI can readily depict even small ischaemic lesions within the first minutes/hours of stroke onset, and has proven to be more sensitive in ischaemic lesion detection than CT.<sup>20</sup> MRI is at least as good as CT with respect to the detection of acute intracranial haemorrhage.<sup>21</sup> Stroke mimics such as seizures, migraines, or encephalopathy are typically not discerned on a non-contrast CT.<sup>22</sup> 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 ischaemic 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 <6 or >6 hours earlier.<sup>23</sup> Patients with 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

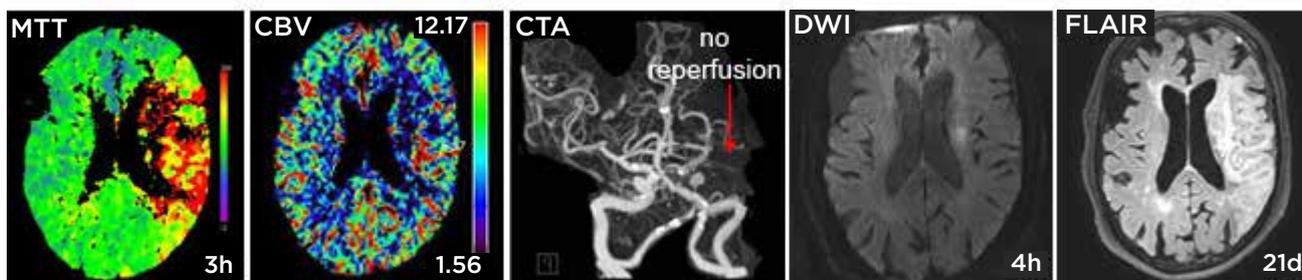
approximately 25% of patients, this concept may significantly increase the eligibility of acute stroke patients for thrombolysis. Despite these advantages of MRI, the applicability to acute stroke patients is often limited due to the required head restraint, difficulties in patient monitoring, and exclusion of patients with pacemakers or claustrophobia.

## THE TARGET MISMATCH

Initially described by Astrup in 1981,<sup>24</sup> the penumbra is tissue at risk of infarction due to a reduction in blood flow, hypoxia, and loss of functionality that has not yet caused irreversible failure of energy metabolism and necrosis.<sup>25</sup> 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 recanalisation 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.<sup>26</sup> The infarct core is the area where MRI-PWI and DWI lesions are overlapping, indicating that hypoperfusion in these areas have already progressed to infarction. With time and 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 >4.5 hours,<sup>27-29</sup> 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.<sup>30-32</sup> These trials (DEFUSE, EPITHET, DIAS-2), although showing a favourable response to thrombolysis with mismatch, could not prove that patient selection for thrombolysis based on the mismatch was beneficial.<sup>2,30,33,34</sup> The results were probably influenced by differences in post-processing of the perfusion maps.<sup>35</sup>

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.<sup>36</sup> 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



**Figure 1: 83-year-old patient presenting with target mismatch without reperfusion, 3 hours after the onset of aphasia and right-sided sensorimotor paralysis.**

The computed tomography perfusion (CTP), including mean transit time and cerebral blood volume maps and the diffusion-weighted imaging-magnetic resonance imaging (MRI) acquired 1.5 hours later, show a target mismatch in a MCA-M1 occlusion. Despite timely start of thrombolysis, recanalisation 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 time to peak on the initial CTP map.

but with a 'malignant' profile, defined as large (>80 ml) DWI and large (>85 ml with  $T_{max} > 8$  seconds) MRI-PWI lesion, recanalisation caused even worse outcomes due to the increased occurrence of parenchymal haemorrhage.<sup>37</sup> These findings suggest that recanalisation strategies should be pursued with caution in patients presenting at later (>3 hours) time points with a MRI-defined malignant profile. Exclusion of patients with a malignant profile and dichotomising into patients with/without a 'target mismatch' demonstrated that patients with a target mismatch indeed respond better to recanalisation therapies, as in the prospective, randomised DEFUSE2 trial.<sup>38</sup>

Currently, several trials are testing the target mismatch as a selection criterion to extend the thrombolysis time window to up to 9 hours or test endovascular recanalisation.<sup>39</sup> 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.<sup>7</sup> 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.

## CONCLUSION

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 delay growth of the ischaemic core. It is conceivable that differences in collateral supply or in tissue resistance to ischaemia might contribute to the observed imaging patterns.<sup>40</sup> If different growth dynamics are to be expected, the influence of time should be incorporated into existing models of infarct growth. Recanalisation 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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