Perfusion Imaging and Stroke

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Magnetic resonance imaging has become an integral part of patient management and clinical research in stroke. As the majority of stroke patients have an ischemic etiology, assessment of tissue perfusion with perfusion-weighted MR imaging can play a major role in diagnosis, evaluation of therapy, and clinical follow-up.

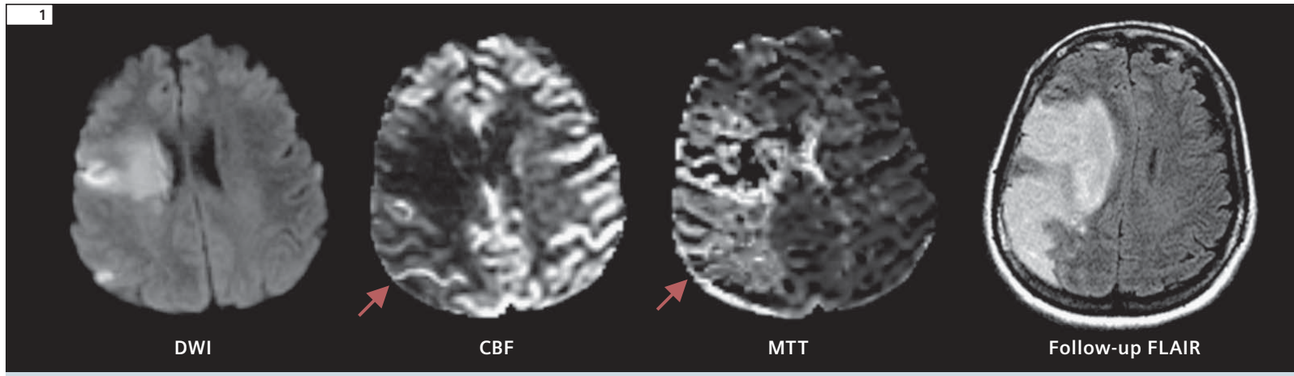
To date, the only FDA-approved pharmaceutical treatment for acute ischemic stroke is recombinant tissue plasminogen activator (rt-PA) [1]. However, in the US and in other countries only a few percent of patients with acute ischemic stroke are treated by rt-PA, typically because of late arrival to medical care (e.g. they arrive later than the requisite time window of 3 or 4.5 hours) [2, 3]. Hence there remains substantial interest in developing novel stroke therapeutics that could be effective in a wider therapeutic window, or to extend the window for thrombolysis into patient populations with delayed presentation. The recent results of ECASS 3 study demonstrate that thrombolysis can be safely applied as late as 4.5 hours in certain well-characterized patients with a resultant improvement in neurological outcomes [4].

The benefit of thrombolysis appears to gradually diminish over time, which has lead to the maxim "time is brain," and in all cases guidelines suggest treating patients as rapidly as possible. However, it has been proposed that the 3 hour or even the 4.5 hour reperfusion window may be too narrow for certain groups of patients [5–8]. This has gained credence as imaging has revealed that the extent of tissue that eventually undergoes infarction varies substantially among stroke patients, with some patients appearing to have a persistent "ischemic penumbra" that might be salvageable well beyond 3 or 4.5 hours [9–11].

How common is delayed presentation? In the US, the rate of rt-PA administration in acute stroke patients hovers around 5%. Because of the time needed to determine eligibility for thrombolysis, an additional 5% could be candidates for treatment if the window were extended to 6 hours [12]. Strikingly, a further 40% of stroke patients present to the emergency department at time greater than 6 hours but still acutely, suggesting that strategies that could extend treatment even into a small subpopulation could have a significant impact. While there is evidence that a substantial segment of acute stroke patients present later than 6 hours and less than 12, how likely is it that they may benefit from delayed thrombolysis? Accumulating data in the literature combined with our own provide tantalizing evidence that time is much less relevant after 6 hours as compared to before. The heterogeneity of this delayed population however, obscures the potential benefit of thrombolysis that certain subsets might experience. Indeed, ECASS 2 showed that minimally selective strategies applied to patients even less than 6 hours did not result in improved neurological outcome and may have even been harmful. Extending treatment to patients in the 6 to 12 hour category would therefore require careful selection.

Which patients might benefit from delayed treatment? While there are few solid data to answer this question, there are some intriguing clues.

One widely used approach to the identification of salvageable tissue is based on a popular hypothesis: regions of mismatch between diffusion-weighted imaging (DWI) lesions and perfusion-weighted imaging (PWI) lesions found on early stroke imaging, that sometimes go on to infarction, but sometimes do not, represent tissue that has an increased likelihood of salvageability. The basis for this thinking is that since brain parenchyma can undergo a period of hypoperfusion without developing permanent parenchymal injury, perhaps this mismatch region is salvageable. This mismatch region is sometimes therefore called an imaging correlate of the ischemic penumbra. The DWI lesion is thought to represent irreversibly damaged area, termed by some investigators to be representative of the ischemic core. This hypothesis has been tested in the DEFUSE study, a prospective study of 74 patients receiving rt-PA therapy between 3 to 6 hours after symptom onset [13]. Patients with a mismatch had significantly increased odds of favorable clinical outcome if reperfusion was attained, whereas no beneficial effect with reperfusion was observed in patients without. These findings support the idea that the mismatch is a useful concept; other single-center retrospective studies based on both CT and MRI mismatches further support the mismatch hypothesis [14–16]. Remarkably, we have found that as many as 40% of our patients in the 6 to 12 hour time frame still have a persistent penumbra defined by DWI/PWI mismatch. Recent analysis reveals that perfusion imaging used to guide delayed IV thrombolysis is associated with



1 Persistent penumbra in 52-year-old male 11 hours post onset of symptoms. Mismatch (red arrows) proceeds to infarction on follow-up FLAIR at 6 days. *Figures reprinted with permission from MRM 50:856-864 (2003).*

increased reperfusion [17]. Interventional approaches have recently demonstrated that good neurological outcomes can be achieved even when revascularization occurs later than 8 hours [18]. Experience in the MERCI/multiMERCI cohort suggests that the time to reperfusion is not adversely associated with outcomes in these delayed patients and that good neurological outcomes are nearly as common early as they are late (~ 40%). Put another way, patients who were reperfused later than 7 hours from the ictus had similar rates of good outcome compared to those with earlier reperfusion [19]. Nevertheless, just over half of these patients did not experience a good outcome and may have been unnecessarily exposed to the risks of the intervention. Similarly, extending thrombolysis into such a delayed population may carry increased risk of hemorrhage. This further emphasizes the importance of characterizing and distinguishing patients who may benefit from delayed treatment from those who would not.

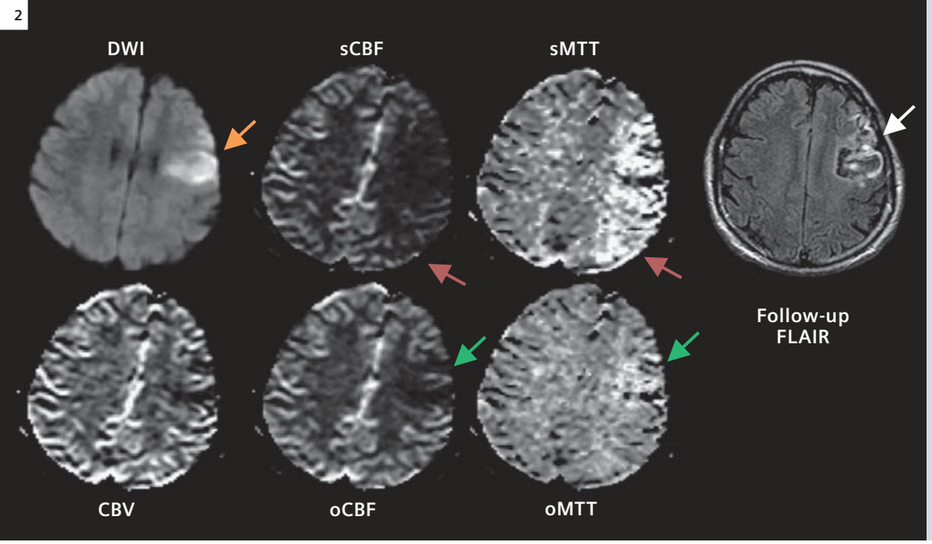
At least two recent trials have investigated the outcome of reperfusion therapy based on PWI/DWI mismatch: EPITHET [20] barely missed its prospectively defined primary endpoint, which was to demonstrate whether patients exhibiting mismatch responded better to late rt-PA therapy than those that did not; DIAS II [21] failed to demonstrate that patients selected using neuroimaging can benefit from reperfusion therapy up to 9 h. While there were methodological issues with both of these trials – particularly with perfusion imaging, which we believe needs to be improved and made less sensitive to delay artifacts – it seems likely that more than DWI/PWI will be needed. While the diffusion abnormality is almost always associated with later infarction, even this is not always the case [22].

Still, the late presence of the DWI/PWI mismatch remains intriguing. We have identified that this mismatch can be highly persistent, lasting for many hours [23], particularly in patients with proximal artery occlusions [24]. But the high variability in tissue and clinical outcome of the treatment based on the mismatch suggests at least two major areas of further research:

- methodological differences in the definition and measurement of the mismatch;
- biological factors playing a role in tissue salvageability.

While the mismatch could be a sign that there is still viable tissue even at late time points – something that PET also has suggested [25, 26] – it also could mean that PWI-based method is unreliable and is actually not useful. Some investigators have suggested that the so-called mismatch might in reality be due to technical limitations that have previously overestimated the size of the penumbra. This leads to the question: Could the persistent penumbra simply be an artifact?

Currently, the measurement of tissue perfusion is based on serial imaging of the concentration of exogenous contrast agent, such as gadolinium-DTPA or endogenous agent, such as magnetically labeled blood [27]. The most common technique is contrast-enhanced dynamic susceptibility (T2*-weighted) technique (DSC), which employs the measurable decrease of signal intensity, as it is seen on a series of rapid images obtained when a bolus of IV contrast agent passes through the brain. This signal intensity decrease can be converted to a concentration-time curve, from which the hemodynamic parameters are then calculated. Cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT), are estimated by deconvolving the change in tissue concentration over the first pass of a bolus of contrast agent with an arterial input function (AIF) using standard singular value decomposition (sSVD) [28]. However, flow estimates using sSVD have been shown to be sensitive to tracer arrival delay (such as might occur with carotid stenosis that caused a delay in tracer arrival but not a decrease in flow), and dispersion between the selected AIF and



2 Artifactual mismatch due to delay-sensitive CBF calculation in a 62-year-old male imaged 7 h after symptom onset. The diffusion lesion (orange arrow) is similar to the 4 month follow-up FLAIR lesion (white arrow). The standard CBF and MTT maps (sCBF, sMTT) show a large mismatch (red arrows); this mismatch disappears when circular deconvolution methods are used (oCBF, oMTT, green arrows). Therefore the correct assessment is that there is no DWI/PWI mismatch in this patient when PWI is correctly computed. *Figures reprinted with permission from MRM 50:164-174 (2003).*

tissue signals [29–32]. This results to a significant underestimation of CBF and therefore, greater mismatch.

We developed a method to compensate this, called circular deconvolution (oSVD), that uses a block-circulant matrix for deconvolution to reduce sensitivity to tracer arrival differences between chosen AIF and tissue signal. Adding the delay parameter to the method (reflecting the disturbed hemodynamics) provides more accurate estimates of CBF and MTT than standard sSVD. Importantly, the oSVD technique gives results comparable to those of sSVD when there are no differences between the tracer arrival time of the AIF and the tissue signal [32, 33].

Another cause of variability is using "global" arterial input function. It is typically selected manually by a trained specialist as the average of a small number of concentration-time curves from voxels immediately adjacent to a major artery in the contralateral hemisphere and then deconvolved from the concentration-time curves for every voxel of the brain. But, if used on a tissue that has delayed and/or dispersed concentration-time curves, this leads again to an underestimation of the blood flow, thus adding another possible source of misinterpretation.

In theory, both delay and dispersion can be overcome by using the so-called "local AIF" method. In this method, an arterial input function (AIF) is defined for each voxel based on the voxels in the local nearby region of tissue. Moreover, this method is fully automated, because the local AIFs can be selected as a part of a predefined algorithm. First results appear promising, though full validation remains to be carried out. As patients with stroke are likely to have delay and/or dispersion, further improvements in delay and dispersion correction methods remain the aim of ongoing research [34].

We note that even with this improved blood flow calculation methodology, more metabolic information may well be needed to understand the concept of persistent penumbra and to truly identify salvageable tissue. We and other groups have already developed models that incorporated other biological variables, such as stroke location, age and stroke subtype [35–37]. These methods take multiple input parameters and allow the system to create "risk maps" that can be used to describe the probability of infarction of each single voxel of tissue, based on acute imaging. Other metabolic-focused approaches, currently being studied in our laboratory and other laboratories, include:

- brief patient exposure to oxygen, and measurement of the tissue response (by, for example, quantitative BOLD imaging);
- use of pH-weighted MR imaging, and correlating these findings with follow-up tissue outcome,
- measuring levels of lactate in both infarcted tissue and penumbra (using an adiabatic high-resolution spiral CSI sequence) to determine their geographical difference and relation to the tissue viability.

Conclusion

Stroke remains a major public health problem throughout the world, and MRI has already contributed substantially to its management. Further efforts are needed to improve perfusion imaging and beyond in order to optimally reduce morbidity and mortality.

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