Perfusion-Weighted Imaging/Diffusion-Weighted Imaging Mismatch on MRI Can Now Be Used to Select Patients for Recombinant Tissue Plasminogen Activator Beyond 3 Hours

Pro

Peter D. Schellinger, MD; Jochen B. Fiebach, MD

“‘It’s now or never. I was caught in a dead end street. A look (into your eyes) can heal me. And after this moment, you gave me something (back). What I really need.’”

Primal Fear, “Nuclear Fire,” 2001

Of course, the “dead end street” refers to computed tomography (CT), “the healing look” to reading a stroke MRI, and being “given something that one really needs” to thrombolytic therapy.

What do we need to establish that a new methodology is ready to be put to use instead of an older one? We need to show that it is at least as good, if not better, than the old modality with regard to safety, feasibility, cost efficiency, and diagnostic and prognostic power. Over the last years, a growing number of reports on the use of multiparametric MRI protocols including diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) for guiding treatment in acute stroke patients have been published.

MRI is safe in acute stroke patients; side effects such as allergic reactions to contrast agent and x-ray load virtually do not exist. Feasibility of stroke MRI is estimated between 75% and 95%, granted, somewhat lower than that of CT. The feasibility of stroke MRI depends in part on how patient instability, and therefore safety concerns, is defined in different centers. When compared with noncontrast CT alone, the cost of stroke MRI is higher; as soon as CT angiography and perfusion CT are added to the CT protocol, the difference in cost is marginal. Again, we admit that cost effectiveness of stroke MRI has not been proven yet.

However, it has been shown beyond doubt that the diagnostic accuracy of stroke MRI for ischemic stroke is significantly higher than that of CT, and for intracerebral hemorrhage, it is equally as good as CT. On the other hand, time to treatment is a very strong prognostic variable within the first 90 to 180 minutes after stroke onset. All recombinant tissue plasminogen activator trials with a time window exceeding 3 hours were negative, suggesting that thereafter, patient selection may be more important than time in combination with an insensitive diagnostic tool.

Several open controlled studies used the PWI/DWI mismatch concept to extend the therapeutic time window for thrombolytic therapy and showed that selected patients profit from treatment. Another series showed that patients who are treated on the basis of stroke MRI criteria within 3 to 6 hours fare at least as well as those being treated on the basis of CT within 3 hours. Finally, the recently presented Desmoteplase In Acute Ischemic Stroke phase II trial illustrated 3 important things. First, it demonstrated that thrombolysis beyond 3 hours works if an appropriate tool (ie, stroke MRI) for patient selection is applied. Second, reperfusion on stroke MRI paralleled clinical outcome, showing that stroke MRI may be used as a surrogate parameter for outcome. Third, the therapeutic effect on clinical and MRI outcomes did not depend on time to treatment, illustrating that patient selection may be more important than time. To prevent time loss where it really counts, CT should be the primary diagnostic tool within 3 hours if a center is not able to provide stroke MRI as fast as CT. In keeping with the times, stroke MRI can and should be applied to guide stroke therapy within institutional protocols outside the 3-hour time window if inclusion in a randomized controlled trial is not possible.

Conclusion

“Who all need it—who. Who all need it—you. Who all need it, who all need it (yes you do). You all breathe it, we all need it. Are you ready for a good time? Are you ready?”

Taken from AC/DC, “The Razors Edge”, 1990

Yes, we are ready for stroke MRI!
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Con

Justin A. Zivin, MD, PhD

My German colleagues claim that MRI can now be used to select patients for tissue plasminogen activator (tPA) therapy beyond the 3-hour time window. I wish that were so. As a clinical investigator, it would make my life much easier. However, I still have important reservations.

The computed tomography (CT) criteria for excluding stroke victims within 3 hours were defined in the National Institutes of Health tPA trial1 as being the presence of an increased density on the image. This is associated with hemorrhage. However, as my colleagues note, “Although never formally assessed, CT is commonly considered the ‘gold standard’ to demonstrate intra-cerebral hemorrhage.”2 Nevertheless, the tPA trials showed that excluding patients with this abnormality leads to demonstrable efficacy of treatment for acute stroke patients. The reason we want to exclude patients with hemorrhage is that a thrombolytic will not be efficacious and may increase the hemorrhage rate.1,3

Now the imagers want to substitute MRI for CT. We would like MRI to provide us with 2 types of information: (1) identification of salvageable tissue, and (2) exclusion of hemorrhage. Unfortunately, at present, we are not sure that MRI can do either. At least 3 clinical trials are currently in progress to find out whether perfusion/diffusion mismatch can be used to select patients with salvageable tissue. However, none of these trials have been published, so I cannot review the data. The claim is that the area in between the adequately perfused tissue and the area that is not adequately perfused is the area of salvageable tissue. However, none of these trials have been published, so I cannot review the data. The claim is that the area in between the adequately perfused tissue and the area that is not adequately perfused is the area of salvageable tissue.

References


Key Words: diffusion magnetic resonance imaging ■ magnetic resonance imaging

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qualitatively measures the presence of contrast material, but that is far from being evidence for potentially salvageable tissue. As opposed to the claims of Drs Schellinger and Fiebach, CT is not the “gold standard” for these purposes; histopathology is. To the best of my knowledge, neither CT nor MRI has ever been calibrated against this true standard. This is a critical missing bit of information, and appropriate animal studies could be done to investigate this issue. The question is not how sensitive MRI is; we know it is reasonably sensitive to detect large (by histological standards) lesions. The question is how specific it is. When a blood vessel ruptures, 2 things happen: (1) a parenchymal hemorrhage is produced, and (2) the tissue supplied by that vessel becomes infarcted. Furthermore, even histopathology during the first few hours after stroke onset cannot identify salvageable tissue, so we have no “gold standard” for that.

We all would love to have a method for measurement of tissue viability that is better than simple time measurement from symptom onset. It is possible that empiric criteria will be identified that will be useful for these purposes, but the studies to prove it have not yet been completed, and it may be impossible. The clinical rating scales we use for our outcome measurements are fairly crude, and a more sensitive and specific test would be highly desirable. But there is no evidence that any type of image can do that. The correlation between image size and clinical deficits is poor. A large lesion in a relatively silent area will not produce much clinical damage, whereas a very small lesion in the internal capsule can produce substantial loss of neurological function. In the end, the regulatory agencies of most countries will require behavioral standards to approve new therapies. Images cannot currently supply this evidence, and it is likely that they never will. I hope that the imagers will come up with something we can use, at least for identification of potentially useful drugs in phase II trials. For now, I remain a skeptic.

References

Key Words: diffusion magnetic resonance imaging  ■ magnetic resonance imaging

Using Mismatch on MRI to Select Thrombolytic Responders
An Attractive Hypothesis Awaiting Confirmation

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Our ability to image the ischemic penumbra in vivo raises the attractive possibility of individualized selection of acute therapy, particularly with thrombolytic agents. In other words, clinicians could potentially use magnetic resonance (MR) mismatch as a physiological tissue clock in acute stroke and allow selection of therapy beyond the accepted time windows. Indeed, this was foreshadowed nearly 25 years ago by the originators of the penumbral concept.1 As indicated by Schellinger and Fiebach, there is a body of evidence from small phase II studies to support this approach.2–4 However, prospective trials are still in progress to more rigorously test this hypothesis, and there remain significant uncertainties about the precise MRI definition of the penumbra. These include the optimal measure of perfusion (eg, mean transit time, \( T_{\text{m}} \), or time to peak), the issues of thresholding of perfusion because of benign oligemia, and the relationship between recanalization on MR angiography and reperfusion on perfusion-weighted imaging.

A further critical question that remains unanswered is the potential for diffusion-weighted imaging reversibility with thrombolysis.5 Hence, it is plausible that some nonmismatch patients might be recombinant tissue plasminogen activator (rtPA) responders. Therefore, when we designed the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) (testing the hypothesis that using mismatch, treatment responders to rtPA can be selected in the 3- to 6-hour window), we elected not to use this as an entry criterion.6 Only by including patients without mismatch in a prospective study can this hypothesis be adequately tested. Interestingly, in the Desmoteplase in Acute Ischemic Stroke Trial6 of desmoteplase 3 to 9 hours, MR mismatch was used as an entry criterion. Conversely, in the nonrandomized Diffusion-weighted imaging Evaluation for Understanding Stroke Evo-
lution study, entry criteria are similar to EPITHET to enable the identification of MR patterns that predict response.

In selecting patients for thrombolysis beyond 3 hours, prediction of risk is as important as prediction of benefit. Hence, additional information required from these prospective trials will include the risk of hemorrhagic transformation in relation to the size of baseline perfusion and diffusion deficits. This emphasizes the uncertainties that exist and that it is premature to use MR treatment algorithms as a selection tool at present.

Hence, although not as skeptical as Zivin, we share his view that a higher level of evidence is required before MR mismatch can be used as a routine clinical tool. However, the concept is so attractive that it seems likely to be useful in some form or other.

“You may say I’m a dreamer, but I’m not the only one.”

John Lennon, “Imagine,” 1977

References


Key Words: mismatch ■ penumbra ■ stroke, ischemic ■ thrombolytic therapy
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