Conundra of the Penumbra and Acute Stroke Imaging
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Multimodal imaging of the brain and vasculature during the hyperacute phase of ischemic stroke is perhaps the “mother of all controversies” in stroke’s modern era. Opposing views are firmly held and often cleverly defended, as is the case with Drs Lyden and Parsons. Let us highlight the facts: (1) time is brain, every minute counts; and (2) the significance of the ischemic penumbra as a potentially salvageable tissue, if reperfusion is successfully restored in a timely fashion, is undisputed. Now, let us address the following questions regarding the potential benefit (or lack of it) from the additional information gained by MRI with diffusion-weighted imaging, perfusion MRI or CT, or CT angiography, MR angiography, or transcranial Doppler.

Is there an added benefit from knowing the vascular anatomy of the patient with stroke who presents within the approved time window for intravenous tissue-type plasminogen activator (tPA)? Knowing the vascular lesion before treatment is certainly helpful but is unlikely to change the management strategy, regardless of the location of the arterial occlusion, during the first 3 to 4.5 hours of stroke onset because there is no evidence to support endovascular intervention as a first-line therapy during this time window, especially when considering the time it takes to get the patient to the angiography suite even at the most advanced stroke centers.1 However, what if the vascular imaging shows no arterial occlusion? Should we still proceed with tPA? Dr Parsons and others argue that distal emboli may be difficult to visualize on vascular imaging and that perfusion imaging is more sensitive in this situations. The outcome of tPA-treated patients with “negative” vascular imaging has been poorly studied and thoughtful investigations of this question are long overdue. Until then, we agree with Dr Lyden that patients with stroke presenting within this time window who meet eligibility criteria for thrombolysis should receive intravenous tPA without delay and that vascular imaging should be performed once tPA is started to determine the nature and location of the arterial occlusion because this may warrant consideration for enrollment into ongoing intravenous tPA and endovascular bridging protocols.

What about penumbral imaging and the “mismatch”? Perfusion imaging can provide an estimate of the penumbral tissue based on the mismatch concept, albeit a number of issues regarding the accuracy of various imaging techniques and thresholds need to be resolved and standardized. Identification of a mismatch can be potentially helpful in 3 ways: (1) to extend treatment to patients who do not qualify for thrombolytic therapy based on current guidelines; (2) to recommend against thrombolysis in some patients who present within the current 3 to 4.5 hours window for futility purposes; and (3) to identify tPA nonresponder candidates for endovascular bridging protocols. To date, attention has focused on the use of perfusion imaging to extend treatment with reperfusion therapy beyond the 3- to 4.5-hour window, and evidence supporting a benefit from using penumbral imaging on improved outcome after stroke is lacking. The use of the mismatch as an imaging criterion to improve patient selection for tPA and other reperfusion therapy is certainly rational. However, response to treatment and clinical outcome are complex processes and involve many variables such as size and location of the infarcted and penumbral tissue, clot composition, initial severity of stroke, age, blood glucose levels, etc. Therefore, equating the mere presence of a mismatch with an indication or response to reperfusion therapy may not always be appropriate. We anxiously await the results of several ongoing trials such as Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND), MR and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), Desmoteplase in Acute Ischemic Stroke Trial (DIAS) 4, and Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) 2 to determine if penumbral imaging can be used to extend tPA treatment or other reperfusion therapy to stroke patients beyond the 3- to 4.5-hour window and to improve their outcome. Little has been published on the use of “mismatch” during the 3- to 4.5-hour window. Perfusion imaging during this time can have potential important therapeutic implications. Data from DEFUSE and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), which studied patients within 3 to 6 hours of stroke onset, show that...
the rates of favorable outcome do not differ depending on reperfusion status in patients with no mismatch, implying that such patients should not be considered for reperfusion therapy. However, the current guidelines and fear of medicolegal suits significantly limit the use of perfusion imaging for individualized selection of thrombolytic candidates during the 3- to 4.5-hour time window. At present and until a randomized controlled trial supports the use of perfusion imaging to effectively select “good” responders to reperfusion therapy, we would only recommend the use of perfusion imaging on an individual case-by-case basis for patients who are otherwise considered not eligible for reperfusion therapy based on current guidelines. This includes patients presenting after 3 to 4.5 hours of stroke onset or with an unknown time of onset. During the 3- to 4.5-hour window, perfusion imaging may be useful for those in whom it is unclear if the neurological deficits are due to a stroke, a seizure (Todd paralysis),2 or a metabolic derangement such as hypoglycemia and in patients in whom the diagnosis of stroke is doubtful after a careful clinical assessment.3 Some might argue that tPA is “safe” in stroke mimics; we agree, but … is this how we want to practice medicine?

We conclude that a “one size fits all approach” to imaging of patients with suspected stroke during the hyperacute phase is inappropriate. In some, noncontrast CT may be all that is needed to make appropriate urgent treatment decisions to be followed by more advanced brain and vascular imaging later on to ascertain the stroke mechanism, pathophysiology, and topography. In others, advanced brain imaging may be required, even during the first 3 to 4.5 hours, to make an informed treatment decision. The thought leaders and future guidelines must reflect this reality to advance stroke care.

Disclosures
None.

References

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