The goal of acute stroke therapy is reperfusion of salvageable ischemic tissue. Acute stroke trials have typically focused on inclusion of patients who present within a short time after the onset of symptoms. The assumption underlying this approach is that the time from symptom onset is a surrogate for the volume of salvageable tissue. It has been estimated that in patients with a large vessel occlusion presenting with acute ischemic stroke, about 120 million neurons die each hour. However, more recent data support the concept that the rate at which ischemic neurons become irreversibly injured after stroke onset is actually highly variable and depends on numerous factors, including the site of occlusion and the extent of collateral circulation. It seems that some patients lose neurons at an alarmingly high rate and that even very early reperfusion may be futile. In contrast, there seems to be a subgroup of stroke patients in whom irreversible ischemic injury evolves over many hours. These patients may be ideal candidates for reperfusion therapies administered at late time points.

Diffusion-Weighted Imaging and Irreversible Injury

Although there has been controversy regarding the accuracy of acute diffusion-weighted imaging (DWI) for identification of irreversible ischemic injury, recent clinical and laboratory studies have confirmed that permanent and complete tissue salvage in regions of early DWI positivity is limited to no more than a few milliliters of tissue in the vast majority of large artery infarcts. Reports of large volume reversal may be explained by the fact that apparent diffusion coefficient (ADC) values transiently rise after reperfusion, but this transient rise does not denote tissue salvage. Therefore, obtaining follow-up imaging within 12 to 24 hours of reperfusion may suggest a reversal of DWI changes that later imaging, or pathological examination, confirm to be irreversible neuronal injury. An additional important concept is that DWI reversal is not an all or nothing phenomenon. It is not uncommon for regions of DWI reversal after reperfusion to subsequently demonstrate subtle abnormalities on delayed T2 or fluid attenuated inversion recovery imaging. On the basis of data from animal models, these subtle lesions seem to represent selective neuronal necrosis rather than infarction. Lesions with lower ADC values also reflect more severe reductions in cerebral blood flow (CBF) and ADC values less than $600 \times 10^{-6}$ mm$^2$/s provide more reliable evidence of irreversible injury than milder ADC reductions. Therefore, although acute DWI lesions can overestimate irreversible injury, the volume of overestimation is rarely >10 mL and consequently a large DWI lesion with low ADC values can be considered a highly reliable indicator that a large volume of irreversible injury has occurred.

Perfusion Imaging and Critically Hypoperfused Tissue

Critically hypoperfused tissue can be defined as tissue with a reduction in CBF sufficient to cause irreversible injury if reperfusion does not occur. A limitation of both perfusion-weighted MRI (PWI) and computed tomography perfusion is that they do not provide quantitative CBF values. Many perfusion imaging techniques identify tissue that is relatively hypoperfused; yet, CBF is not low enough to cause irreversible injury. Therefore, these techniques have had a propensity to overestimate critical hypoperfusion. More recently, specific perfusion thresholds have been applied to exclude ischemic tissue with modest blood flow reduction. Recent studies using perfusion parameters that detected delays in contrast bolus arrival time compared with the nonischemic tissue have generated encouraging results. For example, a $T_{max}$ delay of >5 to 6 s is predictive of ischemic tissue likely destined to irreversible injury if reperfusion does not occur. In addition, a $T_{max}$ delay of 5 to 6 s correlates well with critical hypoperfusion as defined by positron emission tomography. Therefore, patients who demonstrate a mismatch between the volume of the early DWI lesion and an appropriately thresholded PWI lesion are likely to have penumbral tissue.

Clinical Observations

Stroke Centers that routinely perform MRI in acute stroke have noted that some patients with middle cerebral artery or internal carotid artery occlusion rapidly develop very large DWI lesions, whereas other patients with identical vessel occlusion develop large DWI lesions over a considerably longer time period. Patients with rapid DWI growth typically have severe perfusion lesions characterized by very low CBF values and substantial delays in the arrival of a contrast bolus ($T_{max}$ delays >10 s) to the ischemic region. These patients have been referred to as having a malignant profile and can be...
identified by both MRI and computed tomography perfusion. These patients seem to have very poor clinical outcomes even when reperfusion therapy has been administered early. It has been estimated that ≈10% of acute stroke patients who present within 3 hours of symptom onset may have already sustained a large volume of irreversible injury.

**EPITHET and the DEFUSE 1 and 2 Studies**

In the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) studies, patients underwent DWI and PWI imaging before treatment with intravenous tissue-type plasminogen activator (DEFUSE 1 and EPITHET) or endovascular therapy (DEFUSE 2). DEFUSE 1 and EPITHET found that patients with a PWI/DWI mismatch had better clinical outcomes and less lesion growth if reperfusion occurred after intravenous tissue-type plasminogen activator treatment in the 3- to 6-hour time window. An exception to this precept was patients with the malignant profile who demonstrated a very high rate of brain hemorrhage and severe disability/death after reperfusion even if they had a mismatch. Mismatch patients who do not have the malignant profile were termed target mismatch. In a pooled analysis of DEFUSE and EPITHET, target mismatch patients had a 5-fold increase in favorable clinical response at 90 days if they reperfused. For patients who did not have a mismatch, there was no association between reperfusion and clinical outcomes or infarct growth.

The DEFUSE 2 study confirmed the concepts demonstrated in DEFUSE 1 and EPITHET in a longer time window (up to 12 hours from symptom onset). Target mismatch patients who reperfused had a substantial reduction in infarct growth and more favorable clinical outcomes. Among patients who did not have target mismatch, there was no association between reperfusion and favorable outcomes or infarct growth. Of note, in patients treated with endovascular therapy between 6 and 12 hours from symptom onset, the odds ratio for favorable clinical response in target mismatch patients with reperfusion versus those without was 8.5 (95% confidence interval, 2.1–35.1). The robust response to reperfusion in these late-treated patients may be explained by the observation that infarct growth is considerably slower in these late-arriving patients who still have a PWI/DWI mismatch. This slower growth rate implies that less infarct progression will occur during the time required to achieve reperfusion. However, if reperfusion is not achieved, the DEFUSE 2 data indicate that infarct progression continues in these patients and clinical outcomes are poor.

**Conclusions**

Randomized controlled trails are required to conclusively prove that advanced imaging techniques can identify a subset of patients who will benefit from reperfusion therapy at delayed time points. Ongoing studies with these objectives are currently in progress. Validated imaging techniques also have the potential to identify patients who have poor collateral circulation and experience rapid infarct growth. Alternatives treatments, rather than reperfusion, may be more appropriate for these patients.

**Disclosure**

Dr Albers has equity interest in iSchemaView and has received consulting fees from Lundbeck, Covidien, Genentech and Concentric.

**References**


**Key Words:** reperfusion ■ collateral flow ■ diffusion MRI ■ perfusion MRI ■ brain ischemia
Impact of Recanalization, Reperfusion, and Collateral Flow on Clinical Efficacy
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