Reperfusion Versus Recanalization: The Winner Is…

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The terms reperfusion and recanalization are sometimes erroneously used interchangeably when referring to outcomes of thrombolytic or endovascular therapies. Recanalization and reperfusion are neither discrete nor static measures and although achieving one often implies the other has also occurred. Arterial obstructions and perfusion deficits can both evolve independently over time, in the early hours not only after stroke onset but also after therapeutic interventions. Distinguishing reperfusion from recanalization can be challenging in the clinical arena because currently available noninvasive measurements from multimodal computed tomography or magnetic resonance imaging (MRI) have imperfect sensitivity and specificity.

In this issue of Stroke, Cho et al1 address the question of whether reperfusion or recanalization is a better predictor of a variety of outcomes in patients with acute stroke. The authors observed that successful recanalization consistently led to reperfusion of the ischemic territory; however, recanalization was not a prerequisite for reperfusion. Their data support the premise that reperfusion is the more influential of the 2 parameters on both clinical and radiological outcomes.

Cho et al analyzed a prospective database of patients with acute stroke studied with serial MR angiography, diffusion-weighted imaging (DWI), and bolus contrast perfusion imaging, on admission and 3 hours later. Forty-six patients were eligible for their study. The median volume of tissue at risk (perfusion lesion with $T_{max} > 6$ seconds–DWI lesion) was 13 mL, which is modest compared with previous studies of patients with intracranial occlusions and likely reflects the predominance of more distal (M2 and M3) occlusions in the population studied. Recanalization that could be visualized on MR angiography (as measured by arterial occlusive lesion score) was present in 28% of the patients who reperfused. All patients who recanalized also reperfused. Reperfusion occurred in 59%; however, nearly a third of the patients with reperfusion did not have recanalization. Reperfusion status was positively associated with good clinical outcome, penumbral salvage, DWI lesion reversal, limited infarct growth, and final infarct volume. Associations between recanalization and favorable outcomes were less potent.

Higher rates of reperfusion than recanalization are not unexpected, because recruitment of collateral circulation can occur rapidly in the setting of an acute vessel obstruction. For example, the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study 2 (DEFUSE 2) demonstrated improvements in reperfusion status in 51% of the patients who did not recanalize.2 We agree with Cho et al that the higher rates of good outcome in patients with reperfusion without recanalization likely reflect the greater physiological importance of reperfusion. However, each MRI study represents a snapshot of an evolving process. An occluded vessel at a moment in time does not imply that beneficial recanalization did not occur subsequently.

In addition, the relative benefits of reperfusion over recanalization for outcome prediction may in part be accounted for by the strengths and pitfalls of the scores used to classify these outcomes. The vascular grading scores used to assess recanalization and reperfusion have differential sensitivities for proximal versus distal lesions. The lack of correlation between recanalization and good outcomes in MRI or computed tomography–based imaging studies may be the product of artificially imposed thresholds in classifying recanalization status. Cho et al use a dichotomized analysis of the arterial occlusive lesion, which separates patients into 2 groups: those with or without evidence of any distal flow. Therefore, minimal flow across the vascular lesion was classified the same as complete recanalization. Furthermore, because the arterial occlusive lesion is based on observation of slow distal to the occlusion, it is highly dependent on the characteristics of the imaging modality used. This study assesses recanalization with MR angiography, which can overestimate the degree of vessel obstruction.3 In addition, an unobstructed vessel may appear occluded if there is excessive patient motion during scanning. These considerations may explain why assessment of recanalization on MR angiography failed to correlate with favorable clinical outcomes. Association between angiographic imaging and outcomes might be more apparent using more sensitive imaging modalities.

Cerebral perfusion is also not all-or-none; it is a dynamic and graded phenomenon. Clinical improvement after revascularization does not imply complete normalization of perfusion. Dichotomized reperfusion classifications typically designate tissue that improves to less than a prespecified threshold as being successfully reperfused. Reperfusion of a prespecified proportion of the relevant perfusion lesion (such as >50%) is often used to identify reperfusers to facilitate data analysis. However, this does not exclude the possibility that more moderate perfusion delays may have clinical consequences in individual patients. Multiple studies have demonstrated that the there is a graded association between the amount of tissue reperfused and the degree of clinical benefit.4

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As a corollary of the dynamic changes that occur in cerebral blood flow, diffusion lesions also evolve dynamically within the first hours after stroke onset and in response to reperfusion. Cho et al noted DWI lesion reversal in about one-third of patients. However, presumably because of lesion growth in nearby tissue, the median final infarct volume was larger than the baseline DWI volume. Prior studies have shown that DWI reversal observed on MRI obtained shortly after reperfusion is often transient and the volume of permanent reversal is typically smaller than concurrent infarct growth into adjacent tissue. Reperfusion-related hyperemia and concomitant vasogenic edema increase apparent diffusion coefficient values and may transiently mask cytotoxic edema. A considerable portion of the reversible DWI lesion may evolve into FLAIR (fluid-attenuated inversion recovery sequence) hyperintensity on follow-up imaging.

MRI diffusion-perfusion profiles likely reflect the degree of functional collaterals. Cho et al found that patients with reperfusion without recanalization had a low hypoperfusion intensity ratio, which indicates a relatively mild prolongation of $T_{2\text{max}}$. Both the degree of mismatch and the severity of the perfusion deficit influence the amount of reperfusion that occurs, both spontaneously and with therapeutic interventions. For example, in DEFUSE 2 patients treated with endovascular therapy, reperfusion occurred in 85% of patients with the target mismatch profile versus 51% in patients with other profiles. Furthermore, among target mismatch patients in DEFUSE 2 who had complete or near complete (>90%) reperfusion, the favorable clinical outcome rate (Rankin 0–2 at 90 days) was extremely high (75%). These results forecast the results of the recently published Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA) trial that exclusively enrolled patients with target mismatch. EXTEND-IA achieved the highest rates of reperfusion (89% with >90% reperfusion) and favorable outcomes (71%) ever attained in a randomized endovascular trial (J.L. Saver et al, unpublished data, 2015).

So which measure of revascularization is more important? Optimal stroke therapy should result in both recanalization and reperfusion. But if you must choose one, we agree with Cho et al: the Oscar goes to reperfusion.

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References

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