Emerging Therapy Critiques

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MR RESCUE
Is the Glass Half-Full or Half-Empty?

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The timely concurrent publication of Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) with the International Management of Stroke Trial III and the Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) Expansion trials confirmed that endovascular therapy was not superior to standard care for patients with acute ischemic stroke. The novel conclusion from MR RESCUE was that, “...a favorable penumbral pattern on neuroimaging did not identify patients who would differntially benefit from endovascular therapy.” Some have interpreted this finding to support a pessimistic (glass half-empty) view of advanced imaging selection for acute reperfusion therapy. We disagree with this viewpoint and argue that the results of MR RESCUE should not dampen enthusiasm for the concept of imaging-based selection. Key limitations of MR RESCUE that hinder the generalizability of the conclusions of the study include enrollment bias, with a preponderance of patients having large infarct cores, and late times to endovascular therapy combined with very low rates of adequate early reperfusion. Lessons learned from this important study should help guide future trials.

MR RESCUE was a phase IIb randomized, controlled, open-label, blinded outcome, multicenter study. Patients were assigned within 8 hours after the onset of large-vessel anterior circulation stroke to undergo embolectomy (with the first-generation Merci or Penumbra devices) or standard care (37% of patients received IV recombinant tissue plasminogen activator). Based on MRI (80%) or multimodal computed tomography, randomization was stratified according to whether the patient had a favorable penumbral pattern (infarct core <90 mL and substantial salvageable tissue) or a nonpenumbral pattern (large core and small or absent penumbra). Notably, only 118 patients eligible for the primary analyses were enrolled across 22 high-volume North American Stroke Centers over nearly a decade (2004–2011). The median predicted infarct core volume at the time of baseline imaging was exceptionally large: 60 mL (34.1–107 mL). Time from stroke onset to groin puncture was late (mean 6.3 hours), with a considerable delay of 2 hours between start of imaging and femoral puncture. Early reperfusion was assessed only in the endovascular group (using the thrombolysis in cerebral infarction [TICI] score at the end of the procedure). The overall rates of good reperfusion (TICI score 2b/3) were only 27%, considerably lower than the rates obtained in other endovascular studies (typical TICI score 2b/3 rates have been ≈40%–45% using first-generation embolectomy devices). In MR RESCUE, reperfusion was first assessed in both the endovascular and the control groups at 7 days; there was no difference in the rate of late reperfusion, which was achieved in only half of the patients: 23 of 47 (49%) in the embolectomy group versus 20 of 39 (51%) in the standard care group. Based on the low rates of early reperfusion and the essentially identical rates of late reperfusion in both groups, it is not surprising that there was also no difference in clinical outcomes between the endovascular and standard care groups (mean modified Rankin Score [mRS]=3.9 in both groups at 90 days). The overall rate of good clinical outcome (mRS, 0–2) was only 19%, substantially lower than the rates observed in either the Interventional Management of Stroke 3 or SYNTHESIS Expansion trials. This lack of clinical benefit with the first-generation embolectomy devices compared with standard medical therapy, which was demonstrated in all 3 randomized trials, limited the ability of any patient selection method (imaging or otherwise) to identify subgroups that had a differential response to endovascular therapy.

Comparisons Between MR RESCUE and DEFUSE 2

Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE 2) was a prospective cohort study in which patients received an MRI scan before endovascular therapy. Subjects were recruited more rapidly in this nonrandomized study; 138 patients were enrolled at 9 stroke centers over 3 years. DEFUSE 2 demonstrated that patients with a Target Mismatch pattern who had early reperfusion after endovascular therapy had more favorable clinical outcomes;
no association between reperfusion and favorable outcomes was seen in the No Target Mismatch group. It is evident that the patient populations enrolled in DEFUSE 2 and MR RESCUE differed substantially, and both studies likely experienced enrollment bias.

The estimated infarct core volumes in the MR RESCUE favorable penumbral pattern groups (medians, 36 and 37 mL) were substantially larger than the Target Mismatch group of DEFUSE 2 (13 mL).4 These differences may be highly clinically significant based on previous data from the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET), indicating a substantial drop-off in good outcomes once core volumes exceed 25 mL.5 The nonpenumbral groups in MR RESCUE had exceedingly large cores (medians, 108 and 123 mL). Why were these core lesion volumes so different between the 2 studies? We suspect that the most likely reason is that the results of the standard baseline imaging (in particular, the diffusion-weighted imaging sequence) could potentially influence the decision to proceed with endovascular therapy in DEFUSE 2 or determine whether the patient would be randomized into MR RESCUE. Many DEFUSE 2 investigators decided to abort planned endovascular therapy if a very large baseline core lesion was identified on diffusion-weighted imaging (28 of the patients enrolled in DEFUSE 2 did not proceed to angiography).5 This practice was based on the emerging literature that suggests reperfusion may be futile in patients with large diffusion-weighted imaging lesions.5–7

However, in MR RESCUE, it is highly likely that a considerable number of patients who may have fulfilled the DEFUSE 2 Target Mismatch profile were screened and treated with endovascular therapy outside of the trial, rather than randomized. It also seems that MR RESCUE investigators might have had more clinical equipoise for randomizing patients with large core lesions. This hypothesis is supported by the fact that the median core lesion volume in MR RESCUE was considerably higher than in any other trial of reperfusion therapy. Further support for this interpretation is provided by the fact that the overall rates of good functional outcome (mRS, 0–2 at 90 days) in MR RESCUE are very low compared with other similar trials, even in the favorable penumbral group: 14% and 23% for the embolectomy and standard care groups. Although the MR RESCUE authors suggested that patients with a favorable penumbral pattern, particularly in late time windows, may have a good functional outcome, we find this statement misleading because the good outcome rates in the MR RESCUE penumbral patients were much lower than that seen in other comparable trials and were, in fact, similar to the No Target Mismatch group in DEFUSE 2 (day 90 mRS, 0–2; 22%–25%). What happened to patients with a Target Mismatch who were treated with endovascular therapy at the MR RESCUE centers outside the trial? They may have had higher rates of good outcomes with endovascular treatment, perhaps similar to those in DEFUSE 2 (day 90 mRS, 0–2; without reperfusion 33%, with reperfusion 56%).

Penumbral Classification
The automated software program used to classify patients into a favorable penumbral pattern or nonpenumbral pattern for the stratified randomization in MR RESCUE failed, in real-time, to classify 42% of cases.3,8 The definition of the penumbral pattern differed from the more typical mismatch approaches used in other penumbral imaging trials and was based on a very complex voxel-by-voxel algorithm that included measures of the apparent diffusion coefficient, cerebral blood flow, mean transit time, and T\textsubscript{max} for the MRI model. The CT model substituted cerebral blood volume for the diffusion coefficient and added a nonimaging-based parameter: the baseline National Institutes of Health Stroke Scale score.8 It seems that these novel algorithms may not have performed as well as other more commonly used methodologies to identify salvageable tissue.9,10 A benchmark for identification of penumbral patients is differential infarct growth between patients who achieve reperfusion and those who do not. In MR RESCUE, the median absolute infarct growth in penumbral patients who were treated with standard care was only 7 mL. There is a large discrepancy between this actual growth and the predicted growth (median volume of at-risk tissue calculated by the algorithms) of 126 mL. It has been shown that T\textsubscript{max} >6 seconds has good specificity for defining tissue at-risk of progressing to infarction for both MR and CT than the thresholds used in MR RESCUE, and this threshold is being used in several ongoing trials.11–13

Data regarding the proportion of at-risk tissue that had very severe hypoperfusion (eg, T\textsubscript{max} >10 seconds) were not presented. This may explain the somewhat paradoxical finding that the volumes of at-risk tissue in the nonpenumbral groups were much greater (227 and 231 mL) than the favorable penumbral pattern group. Reperfusion of patients with this Malignant Mismatch pattern is likely to be futile, with infarct growth, possible hemorrhage, and poor clinical outcomes.6,14 Given the large volumes of at-risk tissue in the nonpenumbral MR RESCUE group and the substantial infarct growth seen in this group, we speculate that many of these patients may have had a Malignant Mismatch profile, with large volumes of severe unsalvageable hypoperfusion. MR RESCUE highlights the need to continue the quest to standardize (and simplify) core and salvageable tissue definition with advanced neuroimaging.

**A Glass Half-Full**
Because of the limitations discussed above, we do not feel that the MR RESCUE results should dampen enthusiasm for continued research to refine and improve imaging-based patient selection. The results from multiple previous studies remain highly encouraging and strongly suggest that imaging has the potential to play a key role in optimizing patient selection for stroke therapies.5,12,15,16 Future trials should aim for inclusion of patients with smaller infarct core volumes, faster imaging to reperfusion times, and more effective reperfusion strategies. We believe that the glass remains half full, but that there is considerable work left to be done. Advanced imaging approaches should continue to be tested in well-designed clinical trials, both within and outside the current therapeutic time window.

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