WHAT WE KNOW AND WHAT WE DON'T

Mechanical Thrombectomy for Large Core Strokes

A review of available study data with an emphasis on what data are still needed.

BY JAY N. DOLIA, MD; RAUL G. NOGUEIRA, MD; AND DIOGO C. HAUSSEN, MD

In carefully selected patients, mechanical thrombectomy (MT) for proximal anterior circulation large vessel occlusion (LVO) strokes offers one of the most powerful treatment effects in cerebrovascular medicine. However, randomized clinical trials have nearly uniformly treated patients with small ischemic cores (median Alberta Stroke Program Early CT Score [ASPECTS] of 9).[1] Similarly, the recently published trials on MT in the late window have limited their inclusion to strokes with small cores (DAWN study, 7.6 mL [interquartile range {IQR}, 3–8 mL]; DEFUSE 3 study, 9.4 mL [IQR, 2.3–25.6 mL]).[2,3] Considering that these trials demonstrated a number needed to treat between 2 and 2.6 to reduce disability of one patient by at least one level on the modified Rankin Scale (mRS), it becomes evident the study design was stringent and patients with larger cores at baseline may benefit from MT.

Despite the revolution in acute ischemic stroke (AIS) treatment, patients presenting with large ischemic core strokes are commonly not offered MT due to the lack of clinical evidence and concerns for procedural safety, futility, and cost-effectiveness. This opinion has been supported by the 2018 American Heart Association/American Stroke Association AIS guidelines, which indicate that the benefits of MT are uncertain for patients with AIS in whom treatment can be initiated within 6 hours of symptom onset and who have ASPECTS < 6 (level IIB recommendation).[4]

The benefit of MT in the large core baseline stroke population remains elusive. Fortunately, recent studies have hinted at a potential benefit of MT in carefully selected patients when compared to medical management alone.[5-11] Understanding parameters that impact the selection process is essential for achieving better outcomes, minimizing futile reperfusion, and developing future MT randomized clinical trials.

WHAT WE KNOW

Establishing the Safety and Efficacy of Thrombectomy

In 1995, strict selection criteria were required to establish the safety and efficacy of intravenous (IV) tissue plasminogen activator.[12] Similarly, these criteria were considered when developing the selection criteria for MT trials. With the exception of MR CLEAN, which allowed inclusion of patients with ASPECTS 0–10,[13] the design of the MT trials of 2015 was to promote inclusion of patients with more limited ischemic core sizes (ASPECTS > 6 and core volume < 50 mL in SWIFT PRIME and < 70 mL in EXTEND IA).[14-16] These thresholds led to the inclusion of patients with very small cores (uniformly < 10 mL by CT perfusion scans or diffusion-weighted MRI [DW-MRI] and median ASPECTS of 8) in the studies.[1-3] These criteria were applied to the endovascular therapy trials to optimize the chances of a measurable treatment response and reduce the risks of complications related to reperfusion.

The first HERMES meta-analysis revealed that patients with ASPECTS 0–5 had a tendency favoring intervention (common odds ratio [cOR], 1.24; 95% confidence interval [CI], 0.62–2.49; *P* interaction between

ASPECTS and treatment effect = .29). However, only 121 of 1,228 (9.4%) patients included in this analysis had ASPECTS 0–5 and therefore provided limited insight.[1] A CT perfusion subanalysis of MR CLEAN data revealed that in patients with ischemic core ≥ 70 mL who underwent MT, only 8% achieved a good outcome, but 46% achieved a moderate outcome (mRS 0–3).[7] This suggested that the subgroup of large baseline core strokes could potentially benefit from reperfusion treatment. The second HERMES meta-analysis further evaluated the large ischemic core population, which included the five positive MT trials from 2015 and the THRACE and PISTE studies.[17,18] The results from this study showed that patients presenting with ASPECTS 3–5 had a significant benefit from MT (cOR, 2.00; 95% CI, 1.16–3.46). Importantly, not only the sample size (and therefore power) was enhanced, but also proportionally more patients were selected by MRI in this updated meta-analysis, which suggests that more accurate determination of the ischemic core extent could optimize selection. However, when stratifying by ASPECTS 0–4, a higher rate of symptomatic intracerebral hemorrhage (ICH) was found in the MT group (cOR, 3.94; *P* interaction = .025). The data from these studies provide preliminary evidence that carefully selected patients with large core stroke may have a more favorable functional outcome despite a potential higher risk of ICH.[19]

Measuring Ischemic Core

Patient selection for MT is heavily dependent on neuroimaging and the assessment of accurate delineation of the core location and volume. Presently, CT-ASPECTS, CT perfusion, and DW-MRI neuroimaging modalities are commonly used in the acute setting for ischemic core estimation. Although ASPECTS was developed to standardize the extent of ischemic damage and predict functional outcome at 90 days and risk of ICH for use with IV tPA,[20] it has been naturally adopted to predict the functional outcome after MT. Given the relatively limited and variable interrater reliability, patients may be excluded from MT due to a perceived large core. Motion and streak artifacts and sulcal effacement (due to engorged leptomeningeal collaterals) may predispose to a false-positive result (a perceived low ASPECTS on noncontrast CT [NCCT]).[21] Another limitation of ASPECTS core determination is that each of the 10 regions is given equal weight rather that determining the importance of eloquent regions or the volumetric differences of diverse ASPECTS regions.[22] Automated CT perfusion has been utilized to quantify the core and penumbral volume. CT perfusion may be a complement to the NCCT and allow a more precise delineation of the ischemic core. As for NCCT, CT perfusion may under- or overestimate the core size and should be used in conjunction with CT-ASPECTS.[23] DW-MRI can be used for core quantification and is the most accurate method for the delineating ischemic core. However, the concern with MRI is the potential delays (especially important in patients with larger cores, which are expected to have worse collaterals ["fast progressors"]), increased costs, and the lack of widespread availability. Accurately determining core extent and topography are likely critical for optimizing patient selection and neuroendovascular procedural course.

Patients With Large Core Stroke May Benefit From Treatment

The expectations of treatment for patients with larger core need to be kept in mind. The rates of independence will certainly be substantially lower compared to those observed in smaller core patients, but treatment could positively impact the chances of a more favorable outcome. The clinical outcomes of MT in small core strokes have been more frequently measured by the rate of good outcomes (independence as defined by mRS 0–2) at 90 days; however, in the large core stroke population where the ischemic core is substantially larger, the definition of favorable outcome should probably be assessed differently. Several recent studies have looked at the clinical outcomes of MT in large core strokes, and a careful interpretation of the functional outcomes is important.[24] It is unclear what the best measure of outcome should be, independence rates (mRS 0–2), mRS 0–3, mRS shift analysis, or weighted mRS. This also raises the question of MT in preventing the need for hemicraniectomy as a clinical outcome.

Data Based on CT Perfusion Selection

A post hoc analysis of the MR CLEAN study focusing on patients who underwent perfusion imaging found that those with a large core (defined as cerebral blood volume > 70 mL) who underwent MT had better clinical outcomes (whether looking at a dichotomized mRS 0–2, mRS 0–3, or through an overall shift in degree of disability). Eight percent (1/13) of the large core patients allocated to MT had a good outcome versus 0% (0/21) patients allocated to medical care, and 46% (6/13) had an mRS 0–3 versus 10% (2/21) who received medical care. Despite expected higher mortality in the large core cohort (35% [12/34] vs 9% [13/141]; *P* < .005), this study suggested that CT perfusion was a useful selection tool in that population.[7]

Similarly, Rebello et al performed a matched case-control study, which showed a favorable shift in 90-day mRS and favorable mismatch profile (as per automated CT perfusion) in patients with large core who underwent endovascular therapy as compared to medical management (OR, 2.56; 95% CI, 2.50–8.47; *P* = .04). Six of the 24 (25%) patients in the intervention group had good outcomes (mRS 0–2) at 90 days compared to 0 of 23 (0%) patients in the control group (*P* = .04). They also found that MT was associated with comparable rates of parenchymal hematoma type 2 (2 [7%] vs 1 [4%]; *P* > .99), remarkably smaller final infarct volumes (87 [77] mL vs 242 [120] mL; *P* < .001), and a trend toward lower rates of hemicraniectomy (2 [7%] vs 6 [21%]; *P* = .10).[8]

Data Based on DW-MRI

Three series report volumetric diffusion-weighted imaging (DWI) analyses. In a small series, Yoo et al showed that all patients (n = 6) with DW-MRI core > 70 mL had poor outcomes despite MT, including three deaths (50%).[25] However, Gilgen et al reported that one-third of patients with DWI lesion volumes > 70 mL and one-third of patients with core > 100 mL were independent at 90 days.[10] Similar findings were reported in the THRACE subgroup analysis, where 12 out of 53 (22%) patients with DWI volume > 70 mL (based on automated CT perfusion software) had favorable outcome (mRS ≤ 2) at 3 months.[9]

MRI-based studies looking at DWI-ASPECTS showed that successful reperfusion was associated with favorable outcomes with a good safety profile. Manceau et al reported that the optimal threshold of MRI apparent diffusion coefficient was ASPECTS > 2 in a sample of 28 individuals, which was found to be independently associated with good neurologic outcome at 90 days (OR, 6.93; 95% CI, 1.05–45.76; *P* = .04).[5]

Mourand et al evaluated 60 patients with DWI-ASPECTS ≤ 5 and found that rates of independence at 3 months were higher in patients in the MT group than in the control group (30% vs 2.1%; *P* < .001). In the control group compared to the treatment group, hemicraniectomy was performed in 22.9% versus 3.3% (*P* = .002), symptomatic ICH was found in 6.3% versus 5% of patients (*P* = .78), and mortality rates were 47.9% versus 25% (*P* = .01), respectively.[6]

WHAT WE DON'T KNOW

Patient Selection

Clinical markers that best determine which patients with a large ischemic core could safely undergo MT have yet to be defined. Although certain characteristics have been shown to be associated with favorable outcomes (young age, occlusion site, eloquence of region at risk, penumbral size), the evidence remains limited. The optimal imaging selection paradigm is not clear, but accurate delineation of the ischemic core by advanced imaging with CT perfusion or DW-MRI appears reasonable, although this comes at the cost of precious time, which may have a higher impact in this more time-sensitive population.

What Is Considered a Large Core?

The final infarct volume (FIV) is a strong and independent predictor of 90-day clinical outcome of stroke patients. Studies have attempted to shed light on what could be the best FIV discriminator for good outcome and therefore guide selection of patients based on the presentation infarct core. Data from the IV thrombolysis literature have previously indicated that a DW-MRI lesion < 25 mL was the most important determinant of an excellent outcome from thrombolysis.[26] An FIV of approximately 50 mL was then demonstrated to have the greatest accuracy for distinguishing good versus poor outcome after intra-arterial therapy for LVO strokes, and an FIV of approximately 90 cm^3 was found to be highly specific for a poor outcome.[27] More recently, a subanalysis of HERMES data showed a strong correlation between FIV and 90-day mRS for intervention within a 6-hour window; furthermore, it demonstrated that an infarct volume ≥ 133 mL represented a highly specific (95% specificity) threshold for predicting unfavorable outcome (95% CI, 92.3%–97.1%).[28] This indicates that there are patients with larger cores who could potentially benefit from treatment.

It has been demonstrated that age plays a significant role in the impact of the FIV on outcome. One study found a cutoff volume for discrimination of good outcome in patients < 70 years of 49 mL as compared with 32 mL in patients 70 to 79 years and only 15 mL in individuals > 80 years.[29] The concept of age-adjusted tolerability of strokes also seems to apply for patients with larger cores. Mourand et al showed that in patients with a baseline DWI-ASPECTS ≤ 5 who underwent treatment, 37% of patients ≤ 70 years had good outcomes compared with 10% in patients > 70 years (*P* = .02).[6] Similarly, Rebello et al evaluated age-stratified data and reported a significant favorable shift in 90-day mRS in those ≤ 75 years (21 pairs; *P* = .03 for ordinal shift analysis; mRS 0–2, 6 of 17 [35%] patients vs 0; mRS 5–6, 3 of 17 [18%] vs 8 of 18 [44%] patients).[8] Every patient > 75 years had a poor outcome regardless of intervention (mRS < 3 at 90 days).

ONGOING TRIALS

The results of recent studies evaluating MT in large core baseline strokes have shown that some of these patients may benefit from reperfusion. However, controlled studies are necessary to define the safety and efficacy of MT in this patient population. Fortunately, the data analyses from previous studies have provided insight into the neuroimaging modalities, patient characteristics, and infarct volume thresholds to help guide and develop study protocols. Currently, there are three trials evaluating MT in large core stroke: TESLA, TENSION, and IN EXTREMIS.

The TESLA trial seeks to determine the effectiveness of MT versus medical management in patients 18 to 85 years presenting with AIS involving the internal carotid artery (ICA) terminus or middle cerebral artery (MCA) M1 segment, CT-ASPECTS of 2–5, and symptom onset within 24 hours. Primary outcome measure will be utility-weighted mRS.[30]

The TENSION trial seeks to evaluate the efficacy and safety of MT in patients < 80 years presenting with an ICA and or MCA M1 occlusion and CT-ASPECTS or DW-MRI–ASPECTS of 3–5 up to 12 hours from onset compared to medical therapy in up to 714 patients. The primary outcome will mRS at 90 days, with secondary outcome measures looking at independence (mRS 0–2) vs moderate outcome (mRS ≤ 3).[31] An interesting and unique feature to this trial is the secondary outcome measure of quality of life given the current state of dismal outcomes for this stroke population.

The IN EXTREMIS–LASTE trial seeks to evaluate the effectiveness of MT on mRS at 90 and 180 days in patients ≥ 18 years presenting with CT-ASPECTS or DW-MRI–ASPECTS 0–5 (CT- or DW-MRI–ASPECTS 3–5 if ≥ 80 years) within 7 hours from onset of symptoms. Interestingly, there is no upper age limit for enrollment, and there are age-adjusted criteria that consider the evidence from previous studies evaluating the interaction between age, infarct volume, and outcomes.[32]

CONCLUSION

Although the treatment effect of MT in large core strokes may be less substantial than that seen in patients with small core strokes, there is a high probability that carefully selected individuals benefit from MT. Better understanding the clinical and neuroimaging parameters by which to select these patients is imperative, and ongoing clinical trials will hopefully help us to better serve this devastated patient population. ■

1. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387:1723-1731.
2. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378:11-21.
3. Albers GW, Marks MP, Kemp S, et al; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378:708-718.
4. Powers WJ, Rabinstein AA, Ackerson T, et al; American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published errata appear in Stroke 2018;49:e138 and 2018;49:e233-e234] . Stroke. 2018;49:e46-e110.
5. Manceau PF, Soize S, Gawlitza M, et al. Is there a benefit of mechanical thrombectomy in patients with large stroke (DWI-ASPECTS ≤ 5)? Eur J Neurol. 2018;25:105-110.
6. Mourand I, Abergel E, Mantilla D, et al. Favorable revascularization therapy in patients with ASPECTS ≤ 5 on DWI in anterior circulation stroke. J Neurointerv Surg. 2018;10:5-9.
7. Borst J, Berkhemer OA, Roos YB, et al. Value of computed tomographic perfusion-based patient selection for intra-arterial acute ischemic stroke treatment. Stroke. 2015;46:3375-3382.
8. Rebello LC, Bouslama M, Haussen DC, et al. Endovascular treatment for patients with acute stroke who have a large ischemic core and large mismatch imaging profile. JAMA Neurol. 2017;74:34-40.
9. Gautheron V, Xie Y, Tisserand M, et al. Outcome after reperfusion therapies in patients with large baseline diffusion-weighted imaging stroke lesions: a THRACE trial (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke) subgroup analysis. Stroke. 2018;49:750-753.
10. Gilgen MD, Klimek D, Liesirova KT, et al. Younger stroke patients with large pretreatment diffusion-weighted imaging lesions may benefit from endovascular treatment. Stroke. 2015;46:2510-2516.
11. Tisserand M, Turc G, Charron S, et al. Does diffusion lesion volume above 70 mL preclude favorable outcome despite post-thrombolysis recanalization? Stroke. 2016;47:1005-1011.
12. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581-1587.
13. Fransen PS, Beumer D, Berkhemer OA, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. Trials. 2014;15:343.
14. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019-1030.
15. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372:2285-2295.
16. Campbell BC, Mitchell PJ, Kleinig TJ, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009-1018.
17. Bracard S, Ducrocq X, Mas JL, et al; THRACE investigators. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial [published erratum appears in Lancet Neurol. 2016;15:1203]. Lancet Neurol. 2016;15:1138-1147.
18. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2016;88:38-44.
19. Román LS, Menon BK, Blasco J, et al; HERMES collaborators. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. Lancet Neurol. 2018;17:895-904.
20. Pexman JH, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol. 2001;22:1534-1542.
21. Haussen DC, Lima A, Frankel M, et al. Sulcal effacement with preserved gray-white junction: a sign of reversible ischemia. Stroke. 2015;46:1704-1706.
22. Sheth SA, Malhotra K, Liebeskind DS, et al. Regional contributions to poststroke disability in endovascular therapy. Interv Neurol. 2018;7:533-543.
23. Haussen DC, Dehkharghani S, Rangaraju S, et al. Automated CT perfusion ischemic core volume and noncontrast CT ASPECTS (Alberta Stroke Program Early CT Score): correlation and clinical outcome prediction in large vessel stroke. Stroke. 2016;47:2318-2322.
24. Dijkland SA, Voormolen DC, Venema E, et al; MR CLEAN Investigators. Utility-weighted modified Rankin Scale as primary outcome in stroke trials: a simulation study. Stroke. 2018;49:965-971.
25. Yoo AJ, Verduzco LA, Schaefer PW, et al. MRI-based selection for intra-arterial stroke therapy: value of pretreatment diffusion-weighted imaging lesion volume in selecting patients with acute stroke who will benefit from early recanalization. Stroke. 2009;40:2046-2054.
26. Parsons MW, Christensen S, McElduff P, et al. Pretreatment diffusion- and perfusion-MR lesion volumes have a crucial influence on clinical response to stroke thrombolysis. J Cereb Blood Flow Metab. 2010;30:1214-1225.
27. Yoo AJ, Chaudhry ZA, Nogueira RG, et al. Infarct volume is a pivotal biomarker after intra-arterial stroke therapy. Stroke. 2012;43:1323-1330.
28. Boers AMM, Jansen IGH, Beenen LFM, et al. Association of follow-up infarct volume with functional outcome in acute ischemic stroke: a pooled analysis of seven randomized trials. J Neurointerv Surg. 2018;10:1137-1142.
29. Ribo M, Flores A, Mansilla E, et al. Age-adjusted infarct volume threshold for good outcome after endovascular treatment. J Neurointerv Surg. 2014;6:418-422.
30. Clinicaltrials.gov. The TELSA trial: thrombectomy for emergent salvage of large anterior circulation ischemic stroke (TESLA). https://www.clinicaltrials.gov/ct2/show/NCT03805308. Accessed January 15, 2019.
31. Bendszus M, Bonekamp S, Berge E, et al. A randomized controlled trial to test efficacy and safety of thrombectomy in stroke with extended lesion and extended time window [published online August 29, 2018]. Int J Stroke.
32. MOSTE LASTE In Extremis Study. https://www.inextremis-study.com. Accessed February 1, 2019.

Jay N. Dolia, MD
Vascular Neurology Fellow
Emory University
Marcus Stroke & Neuroscience Center
Grady Memorial Hospital
Atlanta, Georgia
jdolia@emory.edu
Disclosures: None.

Raul G. Nogueira, MD
Professor of Neurology, Neurosurgery, and Radiology
Emory University
Director of Neuroendovascular Service
Marcus Stroke & Neuroscience Center
Grady Memorial Hospital
Atlanta, Georgia
raul.g.nogueira@emory.edu
Disclosures: Principal Investigator for Stryker Neurovascular (DAWN trial [no compensation], Trevo-2 trial), Cerenovus/Neuravi (ENDOLOW trial [no compensation]); consultant to Stryker Neurovascular; steering committee member for Stryker Neurovascular (no compensation), Medtronic (SWIFT trial, SWIFT Prime trial [no compensation]), Cerenovus/Neuravi (ARISE-2 trial [no compensation]); angiographic core lab for Medtronic (STAR trial); executive committee member for Penumbra, Inc. (no compensation); physician advisory board for Cerenovus/Neuravi, phenox, Anaconda, Genentech, Biogen, Prolong Pharmaceuticals, Allm Inc. (no compensation), Viz.ai; stock options in Viz.ai.

Diogo C. Haussen, MD
Assistant Professor of Neurology, Neurosurgery, and Radiology
Emory University
Marcus Stroke & Neuroscience Center
Grady Memorial Hospital
Atlanta, Georgia
diogo.haussen@emory.edu
Disclosures: Consultant to Stryker and Vesalio.