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Use of Imaging to Select Patients for Late Window Endovascular Therapy

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The substantial clinical benefits of late window thrombectomy that were recently documented in the DAWN (Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention With Trevo)[1] and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3)[2] studies led to expansion of the treatment window for thrombectomy from 6 to 24 hours in the 2018 American Heart Association stroke guidelines.[3] The new clinical trial data and guidelines have led a large number of stroke centers to begin using advanced imaging with computed tomography perfusion (CTP) or magnetic resonance imaging (MRI) to evaluate patients who present with a possible large vessel occlusion in an extended time window. These techniques can provide quantitative estimates of ischemic core and penumbra without user input and have excellent interobserver agreement. However, these techniques also have limitations, and therefore it is important to review all available imaging data before making a decision to proceed with thrombectomy. The purpose of this article is to discuss the recommended imaging options for selecting patients for late window thrombectomy and to review how to interpret CTP maps and MRI images both before and after reperfusion has occurred.

The new AHA guidelines[3] recommend that DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice; therefore, it is important to understand how these trials selected eligible patients. DEFUSE 3 enrolled patients who could be treated between 6 and 16 hours after last known well, and DAWN enrolled patients who could be treated between 6 and 24 hours. Patients in these trials rarely received tPA (tissue-type plasminogen activator; <10%) because they typically presented beyond the tPA time window. Both trials used the Rapid Processing of Perfusion and Diffusion (RAPID) automated software platform (iSchemaView, Menlo Park, CA) to determine imaging eligibility for all patients. Imaging selection for patients in both DEFUSE 3 and DAWN required either CTP or MRI, with the majority being selected by CTP. Ischemic core volumes were based on a RAPID relative cerebral blood flow (CBF) lesion volume using a <30% threshold or a RAPID diffusion-weighted lesion (DWI) lesion volume with an apparent diffusion coefficient (ADC) threshold of $<620\times10^{-3}$ mm/s. The volume of salvageable tissue in DEFUSE 3 was estimated using the T_{max} perfusion parameter with a >6 seconds (T_{max} >6 seconds) threshold on both CTP and MR perfusion imaging. Subtracting the ischemic core volume from the T_{max} >6 seconds volume provides the mismatch volume and dividing the T_{max} >6 seconds volume by the core volume provides the mismatch ratio. Table 1 summarizes the key imaging selection criteria for both studies.

Estimating the Ischemic Core With CTP

Both DAWN and DEFUSE 3 had restrictions on the size of the estimated ischemic core volume that was eligible for enrollment. For patients screened with CTP, both studies used a relative CBF threshold of <30% of normally perfused tissue to identify ischemic core with the same perfusion analysis software installed at each site. It is important to appreciate that CTP maps do not identify infarcted tissue, they identify regions with blood flow abnormities that can predict tissue fate. For example, in patients with an acute arterial occlusion, CTP can identify tissue that is likely to be already irreversibly injured before this tissue can be identified as hypodense on a noncontrast CT. Several studies have shown that relative CBF maps can provide a reasonably accurate estimate of tissue that is likely to be irreversibly injured in acute stroke patients.[4–6]

An important issue is which CBF threshold is most accurate for estimating the ischemic core in acute stroke patients because the choice of threshold can have a substantial impact on how much tissue is considered to be potentially irreversibly injured. There have been several studies that have addressed the question of which CBF threshold is the most appropriate, and in general, most studies have suggested that thresholds of around <30% to 35% are optimal. For example, in one study, 103 acute stroke patients immediately were taken to MRI after a CTP scan.[5] The DWI lesion was used as the gold standard for identifying the ischemic core. In this study, a relative CBF threshold of <38% of normal best predicted the DWI volume. However, in a few patients (<5%), the 38% threshold significantly overestimated the size of the DWI lesion. For these few patients, the CTP results could give the impression that there was less salvageable tissue than may actually be present. The investigators determined that 30% provided the most accurate threshold that did not overcall the DWI lesion. The median absolute difference in the CBF-based core with the 30% threshold was only 9 mL smaller than the DWI lesion, and there were no significant overcalls.

Prospective validation of the accuracy of the CBF <30% threshold was obtained in the SWIFT PRIME trial (Solitaire

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Table 1. Key Imaging-Based Inclusion Criterial for DEFUSE 3 and DAWN

	DEFUSE 3	DAWN
Ischemic core volume	≤70 mL	≤20 mL if age >80
		≤30 mL if age <80 and NIHSS 10–20
		≤50 mL if age <80 and NIHSS >20
Mismatch volume	≥15 mL and a mismatch ratio of ≥1.8	Not required
Vessel occlusion	M1 or ICA (cervical and intracranial)	M1 or ICA (intracranial and cervical if stent not anticipated to be required)

DAWN indicates Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention With Trevo); DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; ICA, internal carotid artery; M1, the first segment of the middle cerebral artery; and NIHSS, National Institutes of Health Stroke Scale.

With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke).[4] In SWIFT PRIME, which used RAPID with the <30% relative CBF threshold, the ischemic core volume at baseline strongly correlated with infarct volume imaged at 27 hours in patients who achieved reperfusion; the median absolute difference between the observed and predicted volume was 10 mL. In this study, there was virtually no evidence of core overestimation; among patients where the 27-hour infarct volume was smaller than the baseline ischemic core, the median difference was only 4 mL.

Variability between CBF core volumes and tissue that is irreversibly injured can occur for a variety of reasons. One of the most important is how long the CBF abnormality has been present. If reperfusion is not promptly achieved, the final infarct volume may be larger than baseline CTP-based core estimate. In contrast, if the occlusion has been present for only a few minutes, even regions with low CBF will not yet be irreversibly injured, and early reperfusion can result in a transient ischemic attack. Therefore, stricter relative CBF thresholds may be required for patients who are imaged early after symptom onset, and this is the topic of ongoing research efforts.[7]

Estimating the Ischemic Penumbra With CTP

Positron emission tomography scan and Xenon CBF studies, as well as clinical trials, have demonstrated that in acute stroke patients, the T_{max} >6 seconds perfusion parameter can estimate tissue that is likely to be critically hypoperfused (CBF <20 mL/100 g per minute) and is at high risk for progressing to infarction if reperfusion is not obtained.[8–10] The mismatch between the T_{max} >6 seconds volume and the ischemic core volume was used to estimate the volume of salvageable tissue in DEFUSE 3.

It is important to be aware that the T_{max} maps are sensitive to delayed contrast arrival, and in some circumstances, delayed arrival does not imply critical hypoperfusion. For example, in a patient with a chronic carotid occlusion, T_{max} delays may be present despite normal CBF, cerebral blood volume (CBV), and mean transit times.

Evolution of Ischemic Core Estimates Over Time on CTP

One of the most important aspects of CTP to be aware of is that the maps reflect the hemodynamics at the moment that the scan is done. CTP does not provide information about what happened to the patient many hours before the scan. In addition, because ischemic core estimates are based on severe reductions in blood flow, once the blood flow abnormality has improved or resolved, CTP is no longer able to estimate the ischemic core. Figure 1 shows an example of a patient who presents with a left middle cerebral artery occlusion and is scanned at 2 hours after symptom onset. After reperfusion, the ischemic core is no longer visible because the CBF is no longer substantially reduced.

Under some circumstances, leptomeningeal reperfusion occurs even if recanalization does not. If spontaneous leptomeningeal reperfusion occurs after the tissue has already become irreversibly injured, CTP may not be able to identify the ischemic core in the region where leptomeningeal reperfusion has occurred because the CBF may no longer be severely reduced. Figure 2A shows the CTP mismatch map in a patient who was imaged 24 hours after last known to be well. At the time the stroke occurred, CBF was severely reduced in most of the left middle cerebral artery territory; however, by the time the CTP scan was performed, leptomeningeal collaterals had

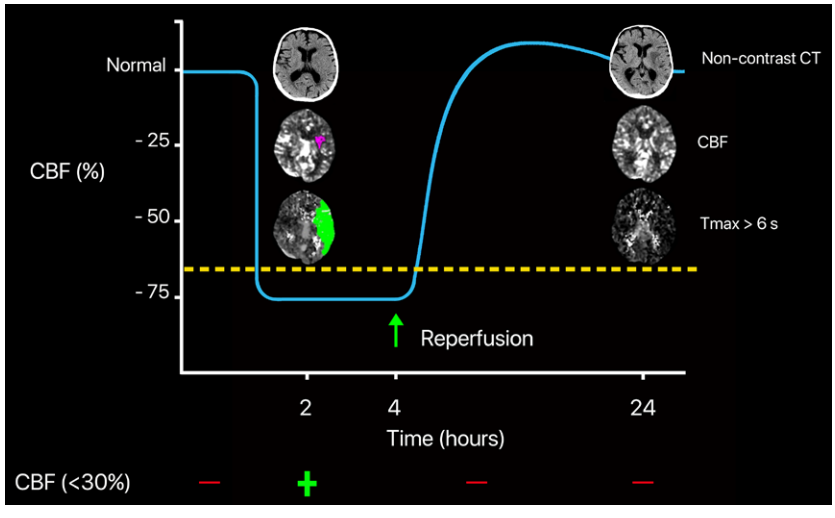

Figure 1. Patient with a left middle cerebral artery (MCA) occlusion. On the baseline scan, the noncontrast computed tomography (CT) is normal. There is a small, deep region in the brain that has low cerebral blood flow (CBF) and is identified in pink (which denotes that the CBF is <30% of normal). There is a large T_{max} >6 s region, shown in green, reflecting the delayed arrival of the contrast agent in the MCA territory. After thrombectomy, there is a substantial increase in the CBF. The green T_{max} lesion disappears and so does the pink CBF lesion; although the tissue is irreversibly injured, there is still blood flow in the irreversibly injured region after reperfusion. Therefore, the ischemic core is no longer visible on the CBF map obtained 24 hours after reperfusion.

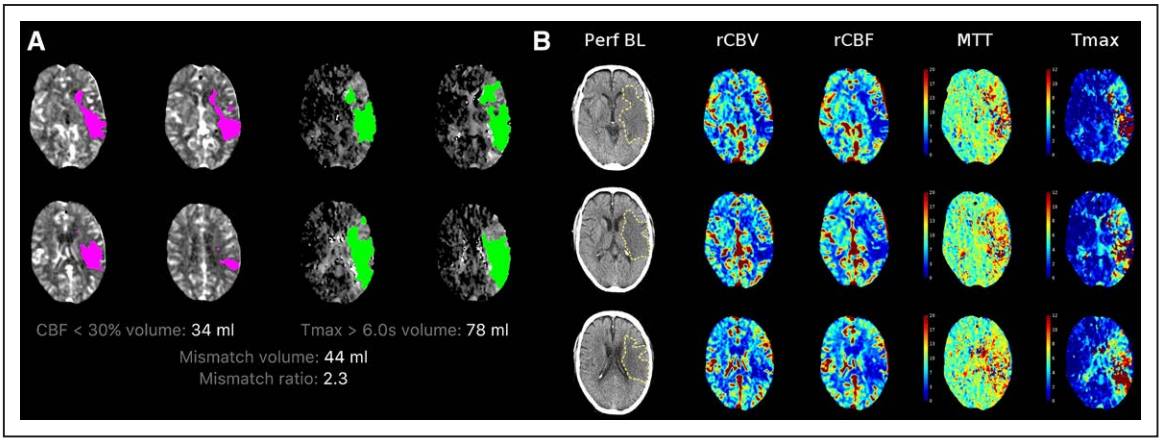

Figure 2. This 75-year-old man was last well 24 hours before presentation with a left middle cerebral artery (MCA) occlusion. His computed tomography (CT) perfusion mismatch map (**A**) demonstrates regions of severe reduction in cerebral blood flow (CBF) in the posterior MCA territory of 34 mL (shown in pink) and significant hypoperfusion of 78 mL (shown in green) resulting in a mismatch of 44 mL. **B**, shows the noncontrast CT scan coregistered to the perfusion images and demonstrates substantial volume of mild to moderate hypodensity in most of the MCA territory (yellow outline) representing a large subacute infarct. The CBF map demonstrates there has been substantial recruitment of leptomeningeal collaterals into the anterior region of infarct, which explains the underestimation of the ischemic core on the mismatch map. rCBV indicates relative cerebral blood volume.

been recruited. Unfortunately, these collaterals came too late; the tissue was already irreversibly injured. However, because the CBF was no longer low in the frontal region, CTP was unable to identify the core in that area. This reinforces the notion that CTP does not image dead tissue, it can demonstrate low blood flow that is likely to be associated with tissue death.

CTP maps are not sensitive for detecting brain hemorrhage. Therefore, a close evaluation of the noncontrast CT is essential to ensure that subacute or chronic infarcts, as well as acute hemorrhage, are not missed.

Technical Issues With CTP

To be confident about the accuracy of CTP volumes, it is important to have a technically adequate scan. CTP analysis programs typically require identification of the flow in a normal vessel that has early arrival of the contrast bolus (known as the arterial input function) and the flow through a venous sinus where the bolus departs the brain (known as the venous outflow function). The scan needs to be long enough in duration to capture the full arterial input waveform, as well as the venous output. In general, a scan time of 55 to 60 seconds is required to account for delayed and dispersed bolus arrival in patients with reduced cardiac output.[11]

Patient movement is the most common cause of CTP artifacts. Artifacts can be minimized by making sure that the patient is tightly secured in the scanner and is relatively calm at the time that perfusion imaging begins. An adequate contrast bolus, with a large bore IV, is also required.

Estimating the Ischemic Core and Penumbra With MRI

If using MRI to select patients for late window thrombectomy, the DWI lesion is the recommended sequence to estimate the size of the ischemic core. Automated software programs typically use an ADC threshold to identify tissue with severely restricted water proton movement. Studies have suggested that an ADC threshold of $<620\times10^{-3}$ mm/s identifies tissue that is highly likely to be irreversibly injured.[12] Just as in CTP, the T_{max} >6 seconds perfusion parameter is often used to estimate tissue that is likely to progress to infarction if reperfusion does not occur. The mismatch between the acute DWI lesion volume and the T_{max} >6 seconds lesion volume estimates salvageable tissue.[8–10]

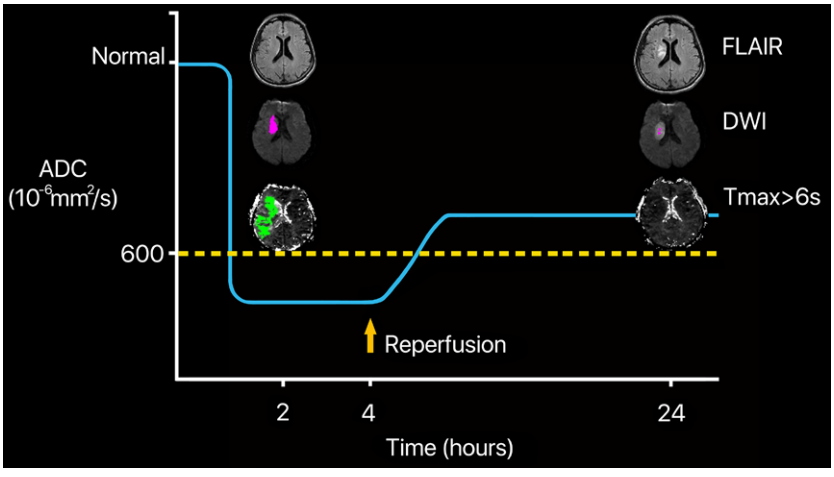

Figure 3. The first set of 3 images was obtained 2 hours after symptom onset in a patient with an acute right middle cerebral artery (MCA) occlusion. The top image, a FLAIR sequence is normal; however, the diffusion-weighted lesion (DWI) map, identifies regions of severe ischemia with low apparent diffusion coefficient (ADC) values adjacent to the right lateral ventricle (shown in pink). On the T_{max} perfusion image, shown immediately below the DWI map, the green region corresponds to a large portion of the MCA vascular territory with severe hypoperfusion. Four hours after symptom onset, the patient experienced complete reperfusion of the MCA occlusion. After reperfusion, the ADC values (shown by the blue line) rise to levels above the ADC threshold (shown with a dotted yellow line) therefore the complete DWI lesion no longer has a low ADC (pink color almost disappears) but typically will still be visible as a bright lesion on both the DWI and FLAIR map.

MRI Findings After Reperfusion

At stroke onset, early cytotoxic edema causes restricted water proton movement, which is reflected by an immediate decline in the ADC value. Reperfusion is associated with an increase in ADC values, even in regions of brain that are irreversibly injured (Figure 3). The magnitude of the rise in ADC values is variable and frequently is nonuniform within an individual ischemic lesion. Frequently, after reperfusion, the ADC increases to values >620×10^{-3} mm/s in part or all of the ischemic lesion. This increase in ADC typically does not indicate tissue salvage. Because of the variable rise in ADC after reperfusion, the volume of tissue with a low ADC frequently underestimates the ischemic lesion that is visible on the DWI or fluid-attenuated inversion recovery (FLAIR) after reperfusion has occurred. Therefore, after reperfusion, infarct volume should be assessed from the DWI or FLAIR maps rather than the ADC volumes.

MRI Findings in Persistent Occlusion

In patients with large artery occlusion who do not experience recanalization, the DWI lesion typically expands into much or all of the persistent T_{max} >6 seconds perfusion lesion.[8–10] However, late window patients, who are selected based on having salvageable tissue, typically have good collaterals, and the final infarct volume may not be obtained for several days.[13] Therefore, a follow-up scan at 24 hours will often underestimate infarct volume in patients who have a persistent occlusion.

Collaterals

Collaterals can be assessed noninvasively with either CT angiography or perfusion imaging. CT angiography was used in conjunction with Alberta Stroke Program Early CT (ASPECT) scores to select patients for the ESCAPE study (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times).[14] This trial enrolled 49 patients beyond 6 hours after stroke onset. The treatment effect in this group favored the endovascular thrombectomy group but was not statically significant in this small group of patients.

Studies have shown that both MRI and CTP maps can estimate the adequacy of the collateral circulation in acute stroke patients. Substantial delays in T_{max} are typically because of poor collateral flow. For example, brain regions with >10 seconds of delay on T_{max} are likely to have poor collateral flow. The ratio of the volume of tissue with T_{max} >10 seconds compared with the T_{max} >6 seconds volume is referred to as the hypoperfusion intensity ratio. A high hypoperfusion intensity ratio, such as ≈≥50%, correlates with poor angiographic collaterals, and these patients have larger baseline ischemic core volumes and more rapid infarct growth.[15] For thrombectomy candidates who are being transferred from a primary center to a comprehensive center, repeat imaging may be warranted for patients with poor collaterals, significant changes in neurological examination, or those with long transfer times. Recent data suggest that an hypoperfusion intensity ratio of >50% can identify patients who are likely to have substantial core growth during transfer.

Assessing the CBV within the ischemic lesion can also predict angiographic collaterals. By comparing the CBV within the T_{max} lesion to the CBV in normally perfused brain regions, a relative CBV ratio can be obtained. Relative CBV has been shown to predict with angiographic collaterals and infarct growth.[16]

MRI Versus CTP for Thrombectomy Selection

Among the modern randomized thrombectomy trials that used advanced imaging for patient selection, both of the late window trials[1,2] and one early window study (SWIFT PRIME) allowed the sites to use either CTP or MRI to select patients.[17] The majority of the patients in these studies were included after CTP. Patients who were enrolled with MRI had similar hospital arrival to femoral puncture times, compared with the CTP selected patients, in all 3 trials. Overall, the MRI-selected patients had a slightly higher rate of favorable outcomes and treatment benefit (Table 2). Despite the small sample size in the MRI subgroups, the primary end point of the studies was statistically significant in both MRI- and CTP-selected patients in both SWIFT PRIME and DEFUSE 3. The treatment effect data has not been published for the MRI versus CTP subgroups in DAWN.

Variability Between Perfusion Imaging Software Packages

Studies have demonstrated that estimates of ischemic core and penumbra can vary markedly between perfusion analysis software packages. For example, one recent study indicated that the correlation between estimated ischemic core volume and final infarct volume in patients who achieved early reperfusion differed substantially between 3 commercially available software programs.[18] Therefore, it is important to use a validated software package when selecting patients for late window thrombectomy.

Table 2. MRI Versus CTP in Early and Late Window Thrombectomy Studies

Study	N	90-d mRS 0–2 Control (%)	90-d mRS 0–2 Thrombectomy (%)	Absolute Benefit (%)
SWIFT PRIME*				
MRI	34	33	63	30
CTP	139	40	60	20
DEFUSE 3†				
MRI	49	19	61	42
CTP	133	16	39	23
DAWN				
MRI	83	35‡		NA
CTP	123	29‡		NA

CTP indicates computed tomography perfusion; DAWN, Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; and SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke.

*SWIFT PRIME was an early window (<6 hours) study.

†CTP and MRI groups had statistically significant treatment effects on the studies primary outcome.

‡DAWN reported pooled data for the thrombectomy and control arms for the MRI and CTP subgroups.

Role of Noncontrast CT for Selecting Patients for Late Window Thrombectomy

Based on the large treatment effect seen in DEFUSE 3 and DAWN, it has been speculated that advanced imaging with CTP or MRI may not be required to select patients for late window thrombectomy. However, currently available data do not support the efficacy of late window thrombectomy for patients selected based on noncontrast CT. For example, in the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) pooled analysis, in which the majority of patients were selected based on a noncontrast CT, often in conjunction with an ASPECT score, the treatment effect diminished over time and was no longer statistically significant just beyond 7 hours after symptoms onset.[14] In the MR CLEAN study (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), that used noncontrast CT alone for parenchymal imaging, treatment efficacy for achieving a favorable outcome (modified Rankin Scale score, 0–2) was lost when stroke onset to reperfusion was longer than 6 hours.[19]

The best data for extended window reperfusion in patients selected by ASPECT scores comes from the REVASCAT study (Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset) that randomized patients to thrombectomy up to 8 hours after onset if the CT ASPECT score was >6 or MR ASPECT score >5. This study showed a substantial reduction in treatment efficacy over time, and favorable outcome rates dropped dramatically for patients with ASPECT scores of 6 to 7.[20] Among these patients, even if reperfusion was achieved, favorable outcome (modified Rankin Scale score, 0–2 at 90 days) rates were <20% if reperfusion occurred >9 hours after the time the patient was last known to be well. In contrast, in DEFUSE 3, favorable outcome rates were 50% in patients who were treated between 9 to 12 hours after symptoms onset, and neither DEFUSE 3 or DAWN showed a decline in treatment effect up to the end of their treatment windows.[1,2]

Conclusions

The only imaging modalities that have been shown to be effective for selecting patients for late window thrombectomy are CTP and MRI. Previous trials using noncontrast CT or ASPECT score selection have documented low rates of good outcome in patients who were reperfused beyond 8 hours from symptom onset. Therefore, as use of advanced imaging increases in both primary and comprehensive centers, it is important to understand how to interpret these images in acute stroke patients both before and after reperfusion has occurred.

Disclosures

Dr Albers has an equity interest in iSchemaView and is a consultant for iSchemaView, Medtronic and Genentech. DEFUSE 3 was funded by the National Institutes of Health (Principal Investigator, Dr Albers).

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Key Words: clinical trial ■ magnetic resonance imaging ■ reperfusion ■ stroke ■ thrombectomy