Defining Intravenous Recombinant Tissue Plasminogen Activator Failure
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Although the 2 National Institute of Neurological Disorders and Stroke (NINDS) trials1 and subsequent studies from Europe (ECASS-3, IST-3)2,3 established intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rtPA) within 4.5 hours of symptom onset as an effective treatment for acute ischemic stroke, the ability of IV rtPA to predictably result in an excellent outcome is still limited; in most cases, IV rtPA treatment is not enough to produce complete recanalization.4,5

Intraarterial (endovascular) treatment (IAT) is superior to IV rtPA in opening arteries, particularly when coupled with mechanical thrombectomy, with recanalization rates up to 87%.6,7 There is increasing evidence that IAT has a therapeutic role in large artery occlusions.8,9 In addition, faster time to angiographic reperfusion is a predictor of good clinical outcome with IAT.10 Thus, there is a need for a quick and accurate strategy to identify IV rtPA nonresponders with large artery occlusion to select those patients who would benefit from IAT.

Mechanical Embolus Removal in Cerebral Ischemia (MERCI), Multi MERCI, and Solitaire With the Intention For Thrombectomy (SWIFT) are just a few of the studies that have used the concept of IV rtPA failure as inclusion criteria to enroll subjects in their studies. But what exactly is the definition of IV tPA nonresponder or failure? To date, there is no clear and consistent designation for this subgroup in the stroke literature. How do the characteristics of the clot influence response to IV rtPA? Is there a time window that should define IV rtPA failure? Should imaging modalities to assess vessel recanalization be used to define IV rtPA failure? Should early clinical change be criteria to differentiate IV rtPA responders from nonresponders? Accurate and rapid identification of IV rtPA nonresponders may result in improved strategies to target and personalize therapy to those patients who we determine are unlikely to recanalize by IV rtPA alone and may result in better clinical outcomes and in a more rational use of endovascular resources.

The Clot
Clot location may be a criterion to help identify those who are likely to be nonresponders to IV rtPA. It has been shown that efficacy of IV rtPA is highly dependent on clot location (66% recanalization rate for distal middle cerebral artery, 35% for proximal middle cerebral artery, and 9% for distal internal carotid occlusions).4,5 The mechanisms behind this observed difference still remain to be elucidated but is probably related to clot burden. Furthermore, the physical composition of the clot may also be useful in identifying IV rtPA nonresponders. Liebeskind et al11 have shown that erythrocyte-rich thrombi are associated with increased computed tomography (CT) density. Kimura et al12 demonstrated that these erythrocyte-rich clots are unlikely to recanalize with intravenous tPA. In contrast, clot that is fibrin-rich may respond better to IV rtPA.12,13 Similarly, others have shown that in patients with the hyperdense vessel sign, IAT seems to be more successful than IV rtPA,14 and that hyperdense vessel sign on CT may predict a favorable response to mechanical thrombectomy.15

Time
Regarding the use of a time cutoff to define IV rtPA nonresponders, transcranial Doppler (TCD) evaluations have demonstrated that recanalization begins 30 minutes after systemic thrombolysis and is usually completed by 1 hour in most cases.16–20 In addition, persistence of proximal arterial occlusion without signs of early recanalization on TCD after rtPA administration is a poor prognostic sign.18,21,22 Mortality rates of 39% have been reported for patients with large artery clots not showing early recanalization within 2 hours of IV rtPA bolus.21 Given these data, an argument could be made for the use of a 1-hour time window for recanalization to define patients as IV rtPA nonresponders.

Imaging
Vascular imaging by TCD, CT angiography (CTA), magnetic resonance angiography, or catheter angiography might be the best means of identifying IV rtPA nonresponders. Some studies have already differentiated IV tPA responders from nonresponders by using catheter angiography.23–25 The advantage of catheter angiography is the ability to directly intervene on a persistent occlusion if identified. However, relying on catheter angiography as a means of determining IV rtPA response would signify that all patients eligible for IV rtPA would have to be taken to the cath laboratory staffed by a neurointerventionalist at all times, clearly an impractical, risky, and costly approach. There are clear advantages of TCD rather than catheter angiography to detect persisting occlusion as a result of its low price, continuous monitoring, convenience to patient, and swift noninvasive nature. One major issue with TCD is that it requires a trained operator to perform the study.
24/7 which is a commodity that may not be available in most stroke centers. CTA and magnetic resonance angiography can give similar information as TCD and more detailed evaluation of the entire cerebral vasculature, including the more distal vessels, veins, and arterial wall, and are more widely available in the emergency department setting than TCD. However, like TCD, these modalities do not allow direct intervention.

CTA seems to be the most available and practical current method for detecting persistent occlusion. However, clinicians need to be mindful not only of the initial radiation exposure of multimodal examination, which normally leads to a radiation dose of 5 to 10 mSv,26 but also the fact that a second scan would likely be needed to assess recanalization. For reference, the average background radiation dose per annum is around 3 mSv. Furthermore, repeat CTA would necessitate 2 contrast loads. CTA with or without CT perfusion can raise the serum creatinine level27–30 and an increased creatinine is associated with increased mortality in stroke patients.31,32 Although magnetic resonance angiography imaging would avoid radiation exposure and the need for iodinated contrast, it can be inaccurate for detection of vessel occlusion or stenosis and does not allow for direct evaluation of the mural thrombus and vessel wall. Also, patient-related factors, such as the presence of a pacemaker, agitation, or hemodynamic instability, can make magnetic resonance imaging unfeasible in patients presenting with acute stroke in an acute emergency setting.

Clinical Course
What are the clinical characteristics of tPA nonresponders? One factor that might play a role in determining IV rtPA nonresponders is hyperglycemia. Hyperglycemia has been constantly correlated with reduced rates of rtPA-induced recanalization in stroke patients.33 Other factors predicting poor outcome after IV rtPA might also be useful. National Institutes of Health Stroke Scale (NIHSS)>10 has been associated with arterial occlusions amenable to IAT.34 However, patients with very high NIHSS and advanced age have low rates of good outcome. These factors have been combined into the Houston IAT score validated by Halleli et al.,34 which emphasizes the negative effect of increasing age, elevated NIHSS score, and serum glucose at baseline. A score of 2 or 3 on this simple 3-point scale predicts poor prognosis after IAT, despite recanalization of the upstream artery. The same sort of relationship using a combination of clinical and radiographic variables might be a more accurate way to predict poor response to IV rtPA.

An improvement in NIHSS by 20% at 2 hours has been shown to be the best predictor of recanalization after thrombolysis. Investigators have argued that 20% neurological improvement at 2 hours is the best predictor of recanalization after thrombolysis and may serve as a surrogate marker of recanalization if imaging evaluation of vessel status is not available.35 However, other studies have shown that after successful arterial recanalization with IV rtPA therapy, lack of early clinical improvement is relatively common (37%). Furthermore, at least one third of patients without early improvement after IV rtPA still achieved good outcomes at 3 months.36 This observation discourages the use of early clinical improvement, or lack thereof, as the sole method to identify nonresponders to systemic thrombolysis.

Conclusions
The definition of IV rtPA nonresponders still remains to be elucidated. We argue that a multifactorial approach might be the best option of identifying this subgroup of patients. Factors that should be used in identifying IV rtPA failures include (1) clot location, burden, and characteristics on CT, especially dense middle cerebral artery sign, (2) lack of recanalization on TCD, CTA, or magnetic resonance angiography by 1 hour after IV rtPA bolus, (3) lack of clinical improvement by 20% or NIHSS>10 1 hour after IV rtPA bolus, and (4) a combination of high glucose, high NIHSS, advanced age, and early CT changes, which signify poor outcome regardless of treatment. These variables should be prospectively explored in patients treated with IV rtPA to determine the quickest and most accurate means to identify IV rtPA failures.

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Disclosures
None.

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