Does “Time Is Brain” Also Mean “Time Is Clot”? Time Dependency of Tissue-Type Plasminogen Activator–Induced Recanalization in Acute Ischemic Stroke

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See related article, p 2734.

Pooled analyses of major randomized controlled trials of intravenous thrombolysis (IVT) in acute ischemic stroke (AIS)1-3 have established the clinical dictum of “Time is Brain”4 because longer times from stroke symptom onset to the initiation of IVT are associated with a lower likelihood of good clinical outcomes at 3 months. Recanalization could be the main mechanism why this time dependency is seen, and the so-called recanalization hypothesis is supported by evidence from a meta-analysis of clinical studies that documented recanalization.5 However, no prospective study to date has demonstrated that indeed shorter onset-to-treatment times (OTTs) result in shorter time to recanalization of an intracranial occlusion, in turn proving it to be the key link to better long-term functional outcomes. Conversely, could this also mean that longer times to treatment produce less recanalization attributable to clot maturation and progression of ischemic injury to brain tissues? Could “Time is Brain” also mean “Time is Clot”? As time is lost, clot wins.

In several pilot single-center studies of real-time monitoring of tissue-type plasminogen activator (tPA) infusion by transcranial Doppler (TCD), both the elapsed time from symptom onset to recanalization6 and the speed of clot lysis7 with IVT thrombolysis were associated with early clinical recovery from AIS as determined by serial National Institutes of Health Stroke Scale assessments. Nevertheless, the effect of the temporal profile of recanalization on 3-month functional outcome after adjusting for potential prognostic factors remains unknown.

In this issue of Stroke, Muchada et al8 provide a perspective on the “Time is Brain” dictum. They evaluated time dependency of tPA-induced recanalization in consecutive patients with AIS attributable to proximal or distal acute middle cerebral artery occlusions. The main findings of this retrospective analysis of prospectively collected data during a 12-year period in a single center indicate that the effect of IVT on early recanalization evaluated by TCD at 1 hour after the end of tPA infusion decreases over time. More specifically, treatment initiation after 270 minutes predicted the lack of recanalization especially in distal middle cerebral artery occlusions. Stemming from the way we diagnose some of these occlusions with TCD (dampered high-resistance flow pattern),9 this finding points to either clot maturation or progression of ischemic injury with no reflow phenomenon, or both.

The authors also observed a trend toward lower recanalization rates in patients with proximal intracranial occlusions treated after 90 minutes. This finding lends further support that patients with proximal occlusions and at least severe strokes should be treated as fast as possible with reperfusion therapies that yield the highest and fastest recanalization rates. These patients should be granted prompt access to comprehensive stroke centers.10 Hence, only OTT and pretreatment National Institutes of Health Stroke Scale score emerged as independent predictors of early recanalization in the pooled sample of proximal and distal middle cerebral artery occlusions treated with IVT by the Muchada et al.8

The observations of Muchada et al8 are in line with a recent Japanese study that showed a negative correlation between OTT and the rate of tPA-induced recanalization on magnetic resonance angiography 1 hour after the end of tPA infusion.11 After adjustment for potential confounders including demographic characteristics, vascular risk factors, stroke severity, and location of occlusion, OTT ≤130 minutes was independently associated with a 3-fold higher likelihood of complete recanalization in comparison with OTT ranging from 131 to 180 minutes. The time dependency of tPA-induced recanalization that has been reported by Muchada et al8 reinforces the findings of a prespecified analysis of Interventional Management of Stroke III (IMS III) trial that evaluated factors that may contribute to delayed angiographic reperfusion in patients with AIS randomized to the endovascular arm.12 IMS III investigators identified a negative correlation between elapsed time from stroke onset to emergency department arrival and the time interval between groin puncture and angiographic reperfusion.12 Interestingly, in another prespecified analysis of IMS III trial, Khatri et al13 concluded that every 30-minute delay in angiographic reperfusion reduced the relative likelihood of a favorable functional outcome at by 15% in unadjusted analysis and 12% in adjusted analysis. The observations of the IMS investigators12,13 in combination with the findings of the Christou et al8 support the hypothesis that the time dependency of the clinical efficacy of acute reperfusion therapies
(both systemic and endovascular) in AIS may be attributed to the time dependency of recanalization of proximal intracranial occlusions independent of the selected therapeutic strategy (IVT, intra-arterial thrombolysis, mechanical thrombectomy using different retrievers, etc). This recanalization hypothesis remains to be further validated by an ongoing multicenter, prospective TCD study that aims to determine whether earlier OTT correlates with shorter time intervals between TPA bolus and complete recanalization and if elapsed time from symptom onset to recanalization is linearly and independently associated with 3-month, favorable functional outcome in consecutive patients with AIS with proximal intracranial occlusions treated with IVT.14

Certain limitations of the study of Muchada et al need to be acknowledged. First, early recanalization has been assessed by TCD that is operator dependent and occasionally limited by suboptimal or absent transtemporal windows. However, it should be noted that a recent multicenter study has established the diagnostic accuracy (>80%) of ultrasound criteria for detection of recanalization during real-time TCD monitoring of intra-arterial reperfusion procedures in consecutive patients with AIS.15 Second, the retrospective design of the present study as well as the lack of a prespecified sample size estimation require a cautious interpretation of the reported findings. Third, the authors did not include all potential confounders including residual flow at the site of intracranial occlusion, stroke subtype, length of thrombus, and degree of collateral circulation in the final multivariate logistic regression model evaluating the time dependency of tPA-induced recanalization. On the contrary, the main strengths of this timely study are related to the large sample size (n=508), the homogeneity of the study population (strict inclusion of patients with middle cerebral artery occlusions), the extensive experience of the research group in neurosonology applications in AIS, and the standardization of the ultrasound protocol for assessment of early recanalization in real time at fixed time intervals.

In conclusion, this study adds to the mounting literature indicating the time dependency of the tPA-induced early recanalization in patients with AIS. The reported findings reinforce the notion that administration of IVT must emphasize speed to result in timely restoration of perfusion to tissues that are still salvageable. They also serve as a reminder that the current mantra “Time is Brain” can also mean “Time is Clot” (ie, clot maturation making it more resistive to treatment). Therefore, better, faster, and safer reperfusion therapies16−18 should be expeditiously tested in ongoing pivotal trials for us to be able to help more patients at centers of all levels of care and in the nick of time.

Disclosures
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References
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