

Evaluation of Cerebral Perfusion in Patients Undergoing Intravenous Recombinant Tissue Plasminogen Activator Thrombolysis

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Abstract

Currently, the indication for thrombolytic therapy using intravenous recombinant tissue plasminogen activator (rt-PA) is restricted strictly to patients with acute ischemic stroke within 4.5 h of onset. The effect of rt-PA declines over time; therefore, we need to minimize the time delay while generating imaging information. The use of cerebral blood flow imaging is not recommended within this time window. Conversely, the balance of efficacy and the risk of bleeding complications differ among patients > 4.5 h after onset. Several ongoing studies are using mismatch concepts to extend the therapeutic time window for rt-PA. Long-awaited reliable software, such as RAPID and PMA, are now available to analyze computed tomography/magnetic resonance perfusion data. Patients with wake-up stroke (WUS) are another group that can be used to expand rt-PA candidates. Diffusion fluid-attenuated inversion recovery mismatch is a promising imaging surrogate to select good candidates with WUS. These trials will cause a therapeutic paradigm shift from time-based to tissue-based strategies in the near future.

Key words: recombinant tissue plasminogen activator, thrombolytic therapy, cerebral blood flow, mismatch, tissue-based strategy

Introduction

Thrombolytic therapy using intravenous recombinant tissue plasminogen activator (rt-PA) is a guideline-recommended grade A stroke therapy in many countries, including Japan,¹⁾ the United States,²⁾ and Europe.³⁾ The effect of this therapy depends on the time of its initiation from stroke onset.⁴⁾ Conversely, a detailed evaluation of cerebral blood flow (CBF) and metabolism generates an understanding of each patient's ischemic pathophysiology, as the brain requires a continuous supply of oxygen and glucose from CBF. Recent advanced neuroimaging techniques enable such information to be obtained within a few hours after stroke onset. However, the more information obtained from imaging, the more time is lost, and the chance of recovery becomes lesser. Thus, we need to consider on a case-by-case basis whether CBF imaging is useful for each patient.

1. Chance of salvage for ischemic tissue by reperfusion therapy

rt-PA thrombolytic therapy is derived from a clear and simple concept, i.e., obtain reperfusion by opening occluded vessels before brain damage becomes irreversible.^{5,6)} The therapeutic time window differs among patients because advancement of the ischemic process depends on the level of hypoperfusion.⁷⁾

The possibility of tissue salvage by reperfusion was shown to depend on residual CBF in a study that enrolled 30 patients with acute ischemic stroke who underwent local fibrinolysis between 3 h and 6 h after onset.⁸⁾ In the study, CBF was determined using single-photon emission computed tomography (SPECT) with ^{99m}Tc-HMPAO (99mTc-hexamethylpropyleneamineoxime). Ischemic tissue with CBF greater than 55% of cerebellar flow may still be salvageable, even with treatment initiated at 6 h after the onset of symptoms. Ischemic tissue with CBF less than 35% of cerebellar flow may be at risk for hemorrhage within the critical time window (Fig. 1). If we focus on the < 3 h area of the graph

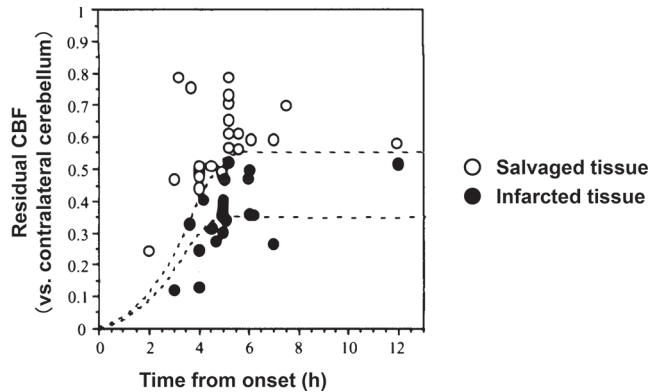


Fig. 1 Possibility of tissue salvage by revascularization in relation to residual cerebral blood flow (CBF). Local residual CBF was evaluated in comparison to the contralateral cerebellum. If the patient is evaluated at < 3 h after onset, there is still a chance for revascularization even with a residual CBF level < 0.5. Conversely, after 4.5 h of onset, a relationship is observed between the degree of CBF decline and tissue outcome. Tissues with residual CBF < 0.35 exhibit a high risk of bleeding. Modified from reference 8.

in Fig. 1, we see that there is a possibility of tissue salvage by timely reperfusion. On the contrary, the > 4.5 h area of the graph shows that the outcome of the ischemic tissue depends mainly on the level of residual CBF. One point we need to learn is that we must focus on shortening the treatment time to within a 4.5-h time window. At the later time window, i.e., > 4.5 h after onset, treatment decision should be made on the evaluation of CBF and tissue viability.

2. CBF imaging within the 4.5-h time window

CBF imaging is not needed in this time window. The 2nd Japanese guidelines for the intravenous application of rt-PA state clearly that diagnostic imaging should be limited to the minimum necessary to avoid unnecessary loss of time.⁹⁾ The presence of early ischemic changes (EICs) should be identified quickly and accurately using non-contrast computed tomography (CT) or diffusion-weighted magnetic resonance imaging (MRI). Residual CBF should be estimated from limited information such as elapsed time from onset, clinical manifestation, size and location of EICs, and the presence of occluded vessels (if available).

The presence of an EIC on CT depends on residual CBF and the time from onset. These are related significantly and independently according to our study evaluating 53 patients with supratentorial acute ischemic stroke in whom ^{99m}Tc-HMPAO SPECT was performed within 6 h of onset.¹⁰⁾ Furthermore, the

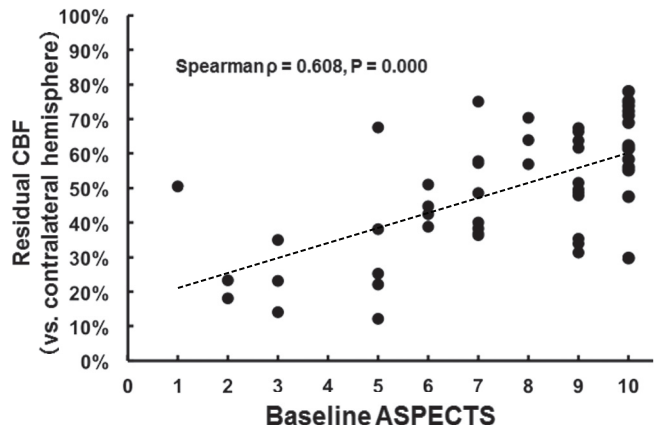


Fig. 2 Relationship between the extent of early ischemic changes and residual cerebral blood flow (CBF). The extent of early ischemic changes evaluated using the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) shows a significant relationship with residual CBF determined by ^{99m}Tc-HMPAO single-photon emission computed tomography (SPECT). For the lower ASPECTS scores, indicating a larger ischemic volume, residual CBF within the ischemic lesion becomes lower. Modified from reference 10.

lower the Alberta Stroke Program Early CT Score (ASPECTS), a semi-quantitative standardized method for EIC evaluation, the more severe the degree of hypoperfusion (Fig. 2). It is estimated that patients with large EICs have an ischemic core with very low CBF, resulting in a high rate of symptomatic intracranial hemorrhage (sICH). In fact, the odds for sICH risk were calculated as 2.2 for every 1 point decrease on ASPECTS among 103 patients enrolled in the Japan Alteplase Clinical Trial.¹¹⁾

A recent topic of EICs is the presence of isolated cortical swelling (ICS) without concomitant parenchymal hypoattenuation (Fig. 3), which is a subtype of EIC that differs from tissues exhibiting parenchymal hypoattenuation.^{10,12,13)} Generally, brain tissue exhibiting EICs is thought to be damaged irreversibly, but tissue with ICS preserving gray-white matter differentiation might have a chance of recovery with timely reperfusion.¹²⁾ We need to evaluate carefully whether the CT density differ between gray- and white-matters. One possible explanation for ICS pathophysiology relates to the enlarged cerebral blood volume that compensates for reduced perfusion pressure.¹³⁾ Another explanation is the timing of CT evaluation, which is performed too early to show any change in CT value.¹⁰⁾ ICS should be excluded from the ASPECTS evaluation because it is believed to contain ischemic penumbra,¹²⁾ although this concept is yet to be confirmed.

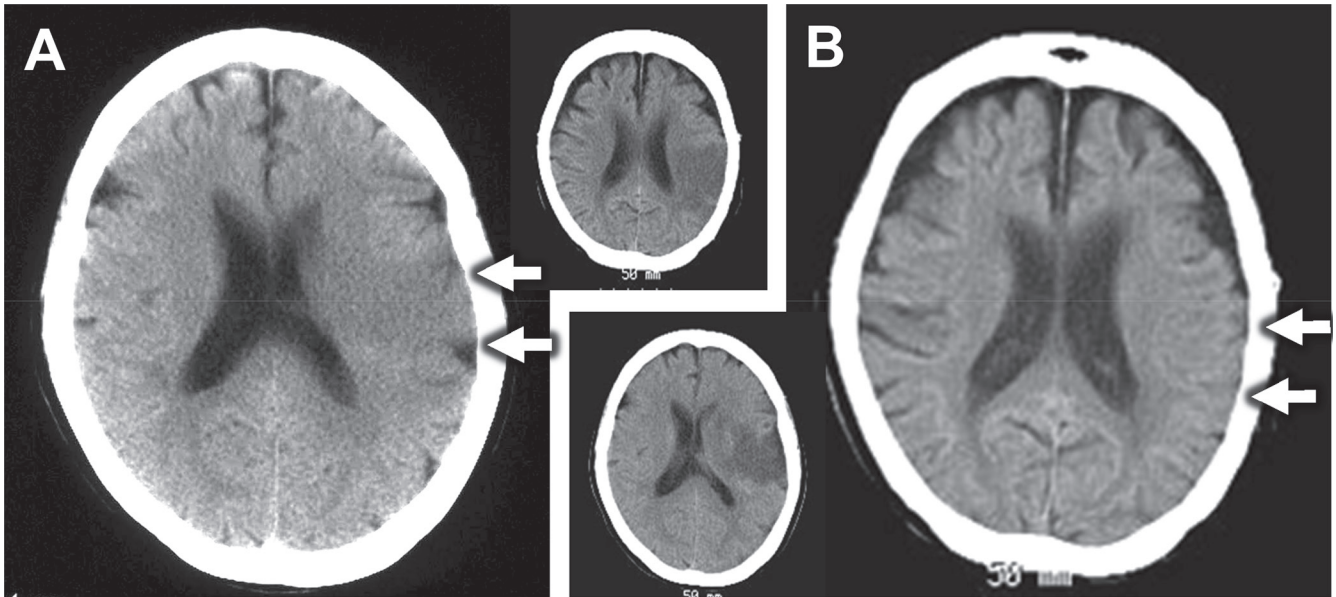


Fig. 3 A subtype of early ischemic change observed on computed tomography (isolated cortical swelling). Two patients with left middle cerebral artery embolic stroke are shown. Both images present with cortical swelling (arrows). The cortical computed tomography density in the area was decreased and preserved in patients A and B, respectively. Both patients were excluded from acute revascularization and exhibit a cortical infarction (small figures). Isolated cortical swelling, shown in patient B, is now thought to contain salvageable tissue. Parenchymal hypoattenuation, shown in patient A, is thought to have irreversible damage.

3. Decision making for rt-PA thrombolysis beyond 4.5 h after onset

Whether or not the patient should be treated with revascularization depends on how much salvageable tissue still exists. In this situation, neuroimaging plays a critical role in making a treatment decision. A mismatch between irreversibly damaged tissue, such as diffusion high-signal lesions and tissue with decreased CBF, shown on CT perfusion or MR perfusion images, which could be salvaged by reperfusion therapy, is used increasingly in clinical studies. Among these, diffusion-perfusion mismatches (DPMs) on multimodality MRI are attracting attention.

Both the Echo-Planar Imaging THrombolytic Evaluation Trial (EPITHET)¹⁴⁾ and Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE)¹⁵⁾ enrolled patients with acute stroke between 3 h and 6 h of onset. These trials showed patients with a small core and DPM are good candidates for thrombolytic therapy. The definition of DPM employed in these trials was: (1) diffusion-weighted imaging (DWI) lesion volume < 70 mL, (2) DPM lesion volume > 10 mL, and (3) perfusion-weighted imaging (PWI):DWI ratio > 1.2. Such criteria have extreme clinical importance to patient selection; however, this has yet to be validated formally.¹⁶⁾

In addition, the classical penumbral concept with the preservation of an annular pattern of mismatch surrounding the infarct core, has been shown to present within the early hours after stroke onset.¹⁷⁾ After that point, a dissociation between DWI and PWI lesions occurs over time (Fig. 4).¹⁸⁾ In other words, the classical mismatch pattern fragments in a time-dependent manner, because of partial reperfusion of DWI positive tissues.¹⁷⁾ Therefore, a simple subtraction of DWI volume from PWI lesion volume will underestimate the true penumbral volume (Fig. 5). Using a three-dimensional (3D) co-registration method, in fact, re-analysis of the data from EPITHET showed a significant reduction in infarct volume expansion when rt-PA was administered to patients with 3D-proven DPM.¹⁹⁾

An international collaborative consortium on acute stroke imaging including Japanese and American researchers is currently working on evaluating and improving the accuracy and/or reproducibility of the CT/MR perfusion imaging technique. As a result, reliable and accurate automated analysis software, such as RAPID developed at Stanford University or PMA by ASIST-Japan, is now available for clinical use. Two identically designed randomized controlled trials, EXtending the time for Thrombolysis in Emergency Neurological Deficit (EXTEND)²⁰⁾ and European Cooperative Acute Stroke Study 4, are

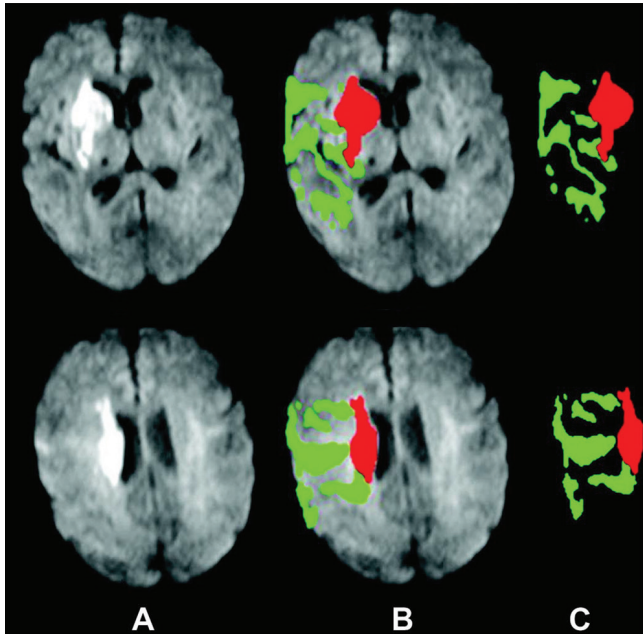


Fig. 4 Example of non-classical pattern of mismatch. Representative case showing fragmentation of the co-registered mismatch lesion. **A:** Diffusion weighted-image (DWI). **B:** DWI abnormal lesion (*red*) and hypoperfusion lesion (*green*) superimposed on DWI. Note fragmentation of the pattern. **C:** DWI abnormal lesion and hypoperfusion lesion with brain image (DWI) removed. Adopted from reference 18 with permission.

now underway and include RAPID-defined DPM patients with stroke within 9 h of onset.

4. Expanding the indication for unknown onset stroke: establishing a tissue-based strategy

Patients who notice their symptoms upon waking, i.e., wake-up stroke (WUS), are also to be enrolled in the EXTEND trial. Although approximately 25% of acute stroke patients suffer from stroke symptoms with an unclear onset time or onset during sleep,^{21–23} such patients are usually excluded from rt-PA thrombolysis as the time of onset is defined by the guidelines to be the last known well time. However, these patients reportedly have similar early ischemic findings on initial CT or MRI as those presenting with a clear onset time within 3 or 6 h of symptom recognition.²⁴ In addition, all subtypes of stroke have an early morning peak, indicating that patients with WUS might be within the time window for rt-PA thrombolysis. In the trial, DPM will be used to identify patients likely to benefit from treatment. The paradigm shift from a time-based strategy to a tissue-based strategy is the most exciting topic of recent acute stroke research.

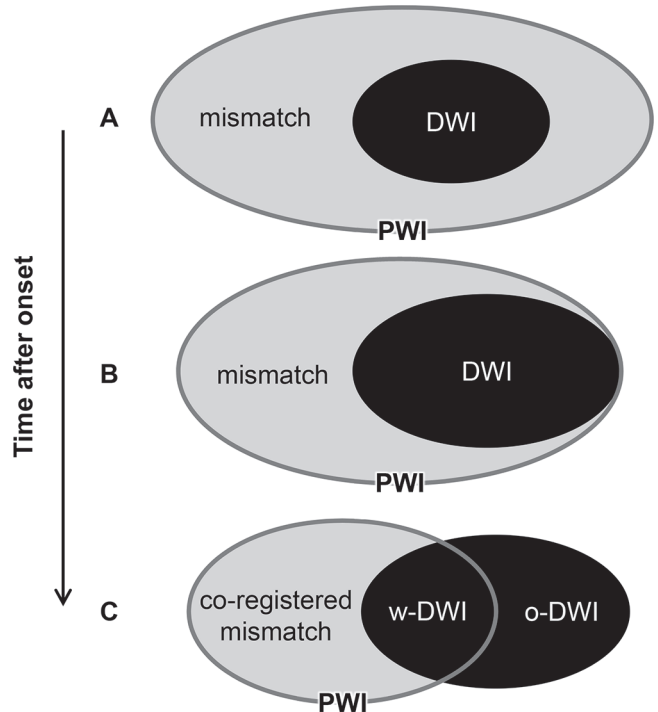


Fig. 5 Topographic relationship between the ischemic penumbra and core. Diagram of the position between high-signal lesions on diffusion-weighted magnetic resonance imaging (MRI) and abnormalities on perfusion-weighted (PWI) MRI. As the time from onset increases (A, B, C), the diffusion-weighted imaging (DWI)-abnormal area (equivalent to the ischemic core) expands and the PWI-abnormal area shrinks. As shown in example C, an ischemic core may be present outside of the PWI-abnormal area (o-DWI). In this case, penumbral volume is the PWI-abnormal zone subtracted by the core (w-DWI), which is inherent therein ($PWI - w-DWI$). A simple subtraction ($PWI - [w-DWI + o-DWI]$) leads to an underestimation of the true penumbral volume.

Another approach to identify candidates for rt-PA thrombolysis, is the utilization of a DWI-fluid-attenuated inversion recovery (FLAIR) mismatch (Fig. 6). This concept depends on the hypothesis that signal changes on FLAIR remain invisible until 4.5 h from onset.²⁵ Previous reports, including one from Japan,²⁶ showed rt-PA thrombolysis was effective in such FLAIR-negative patients if the ischemic core, i.e., high DWI signal, remains small enough. Several multicenter prospective studies are currently ongoing internationally, such as efficacy and safety of MRI-based thrombolysis in WUS in the European Union²⁷ and THrombolysis for Acute Wake-up and unclear-onset Strokes in Japan.²⁸

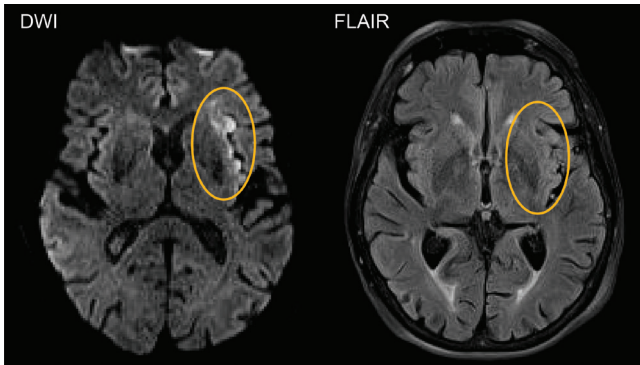


Fig. 6 Example of diffusion-weighted imaging fluid-attenuated inversion recovery (FLAIR) mismatch. Differences of ischemia detection sensitivity between FLAIR and diffusion-weighted magnetic resonance imaging (DWI) can be used to predict the time from onset. Ischemic signal changes on FLAIR are observed rarely within 4.5 h of onset. Thus, among patients with wake-up stroke, those with positive DWI and negative FLAIR are candidates for thrombolytic therapy.

5. Novel thrombolytic agents and CBF imaging

Currently, alteplase is the only thrombolytic agent available for clinical use. However, several problems, such as a short half-life, neurotoxicity, and low fibrin specificity, have been reported. Two possible alternatives that improved these problems are currently under development utilizing CBF imaging.

Desmoteplase, with the same structure as the plasminogen activator present in the saliva of vampire bats, has a longer half-life than alteplase and exhibits no neurotoxicity. The phase II clinical trials Desmoteplase In Acute Ischemic Stroke (DIAS)²⁹⁾ and Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS)³⁰⁾ have generated promising results; however, a phase III trial (DIAS-2) failed to show efficacy or dose-dependency.³¹⁾ Several problems have been discussed. One significant factor is that imaging diagnosis was not standardized across facilities. In fact, integrated analysis of DIAS/DEDAS/DIAS-2 showed a therapeutic effect in a particular group of patients whose absolute difference in DPM was > 60 mL.³²⁾

Tenecteplase is another novel thrombolytic agent modified from alteplase using genetic engineering techniques. It shows high fibrin specificity and strong resistance to plasminogen activator inhibitor-1. The Tenecteplase versus Alteplase for Acute Ischemic Stroke study enrolled 75 patients with acute ischemic stroke within 6 h of onset, who were selected on the basis of arterial occlusion and CT perfusion.³³⁾ Compared to the alteplase group, patients in the

tenecteplase group showed improved reperfusion rates and neurological improvement in a dose-dependent manner. In this study, the ischemic core was defined as < 45% of the contralateral CBF. In addition, the penumbral area was defined as a prolonged mean transit time > 125% of the contralateral side. Using these criteria, a phase III trial, Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation, is currently ongoing targeting patients with stroke within 4.5 h of onset.

Conclusion

Toward the expanded indication for rt-PA thrombolysis, penumbra evaluation using CBF imaging is in the limelight. However, even in the era of a tissue-based strategy, time should never be wasted relying on imaging findings.

Conflicts of Interest Disclosure

The author declares no conflict of interest regarding this review article.

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