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Fibrinolytic Treatment of Acute Stroke: Are We Treating Reversible Cerebral Ischemia?

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With increased understanding of the underlying pathophysiology of acute ischemic stroke, advances in imaging and interventional techniques, and the development of new fibrinolytic and neuroprotective agents, potential therapeutic options in the treatment of patients with acute ischemic stroke have become available recently (1–10). Animal studies have indicated that each minute of ischemia is harmful (11). It is generally believed that the sooner we begin to treat the brain after ischemic stroke, the better are our chances of minimizing the damage: the “time is brain” theory (National Stroke Association newsletter, 1993, 10:1). This has stimulated the drive to treat ischemic stroke as an emergency (“brain attack”).

Emergency treatment focuses on the first 6 hours after the onset of ischemic stroke symptoms. It generally is agreed that the 6-hour time period provides a therapeutic window of opportunity during which medical intervention can be initiated to limit brain damage. Within this window (6 hours), it is presumed that most, if not all, ischemic tissue will remain viable and, theoretically, can be revived. Furthermore, the purpose in choosing a therapeutic window for early intervention is not only to rescue the reversible ischemic tissue but also to avoid complications caused by the reperfusion of irreversibly damaged or necrotic tissue.

The article by Lanzieri et al (12) in this issue reports that the urgent application of thrombolysis in eight patients with middle cerebral artery occlusion using intraarterial urokinase within 6 hours of the onset of symptoms resulted in a statistically significant positive change in National Institutes of Health (NIH) score by at least five points compared with 26 untreated patients

with middle cerebral artery occlusion. A statistically significant benefit of intraarterial urokinase initiated within the therapeutic window was noted. Although the NIH stroke scale is one of impairment, not of disability or outcome, their data suggest that the therapeutic benefit of fibrinolysis in treating acute ischemic stroke is real. They conclude such techniques can be cost-effective in the treatment of patients with acute ischemic stroke.

Also in this issue, Jansen et al (13) report different results. They studied 32 patients with acute internal carotid artery occlusion treated with intravenous recombinant tissue plasminogen activator (rtPA, alteplase) and intraarterial alteplase or urokinase within the first 6 hours after the onset of symptoms. Their data showed no significant benefit from either intraarterial or intravenous thrombolytic treatment even when fibrinolysis was initiated within the therapeutic window. Their data further suggest that thrombolytic therapy did not work and may even have made the patient’s condition worse. They suggested that more-potent pharmaceutical agents or other means such as mechanical thrombectomy may improve outcome. They also speculated that the existence of sufficient collateral circulation before the onset of ischemic stroke is an essential factor that may affect outcome.

The inconsistency between the two articles and many previous reports regarding the efficacy of fibrinolysis in the treatment of acute ischemic stroke was not unexpected (14–17) (Haley EC, Levy D, Sheppard G, et al, “A Dose-Escalation Safety Study of Intravenous Tissue Plasminogen Activator in Patients Treated from 90 to 180 Minutes from Onset of Acute Ischemic Stroke,” *Ann Neurol* 1990;28:225 [Ab-

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stract]) (Brott TG, Haley EC, Levy D, et al. "Safety and Potential Efficacy of Tissue Plasminogen Activator (tPA) for Stroke," *Stroke* 1990;21:181 [abstract]). Recent articles by Ferguson and Ferguson (18) and del Zoppo et al (19) clearly outline many potential problems in the designs and performance of previous studies, possibly contributing to the lack of data to confirm the theoretic benefit of fibrinolytic treatment. Ferguson and Ferguson (18) pointed out that previous studies of fibrinolytic treatment of ischemic stroke suffered from imprecision and inadequate control of systemic errors, negating conclusions regarding clinical outcome. In the absence of convincing data, there is an urgent need to design a clinical trial with strict criteria and standardized protocols to compensate for variables that influence outcome. These include issues related to patient selection, classification of ischemic injury, vascular territories, drugs involved and their dosages, and duration and route of administration of thrombolytic agents (18, 19).

While the medical community attempts to optimize the protocol that will provide sufficient data to validate the usefulness of fibrinolysis in the treatment of ischemic stroke, perhaps (not to add to the complexity of the issue) we ought to consider additional variables that may influence outcome. We are aware of anecdotal reports of cases in which, despite the fact that recanalization was successfully achieved within 15 minutes as demonstrated by posttreatment angiography (such as an iatrogenic clot during a routine angiographic procedure), neurologic deficit persisted. Resolution demonstrated on the image of an angiogram does not necessarily result in a resolution of the patient's symptoms. Conversely, other anecdotal reports described cases in which symptoms resolved completely or the patient had minimal neurologic deficit despite the initiation of fibrinolysis many hours beyond the proposed "therapeutic window."

In the past, we paid little attention to what was happening to the ischemic tissue (end organ) before the recanalization procedure. Has the target ischemic tissue been severely injured beyond recovery or can it be saved (reversible ischemia)? In fact, the viability of the tissue of the end organ, not the angiographic evidence of recanalization, correlates better with clinical outcome. In this commentary, we wish to explore further the critical issues such as tissue viability/reversibility; collateral circulation, par-

ticularly at the microvasculature level (<100 μm); therapeutic window and its associated complications and causes; and potential benefits from the new imaging techniques.

What may affect the viability of tissue and reversibility of ischemia? We believe that regional cerebral blood flow and its collateral circulation are the key factors. Complete blockage of cerebral blood flow can cause irreversible damage, resulting in cell death (necrosis). However, complete cessation of regional cerebral blood flow occurs infrequently in the clinical setting, because collateral flow is recruited from other arterial sources (20). There is no quick and easy way to evaluate the collateral circulation of regional ischemic tissue by conventional radiologic means. Therefore, the viability of tissue and reversibility of the ischemia usually are not predictable, particularly within the therapeutic window.

One key element, the critical threshold for regional blood flow to maintain the neuronal function and viability, has been well studied in an awake primate model (11). When local cerebral blood flow falls below about 23 mL/100 g per minute, reversible paralysis begins. Primates with brief occlusions tolerate marked ischemia without evidence of infarction. When local cerebral blood flow falls below 10 to 12 mL/100 g per minute for 2 to 3 hours, irreversible local damage is observed.

Furthermore, the infarction (critical) threshold does not remain constant (10 to 12 mL/100 g per minute) during the period of ischemia. It gradually rises over 3 hours to a plateau of about 18 mL/100 g per minute (11). When ischemia is prolonged, tissues with inadequate local collateral circulation may suffer irreversible damage more frequently and quickly (shorter therapeutic window) than tissues with richer collateral circulation. For tissues with minimal collateral circulation, irreversible damage may have occurred within the early part of the therapeutic window after vascular occlusion, and fibrinolysis may not improve clinical outcome even if recanalization is achieved shortly afterward.

It is reasonable to believe that the rising critical threshold over time also may vary among individuals. It may depend not only on how much cerebral blood flow the ischemic tissue receives, but also on how much reserve regional cerebral blood volume the tissue has (Crosby DL, Yuh WTC, Magnotta VA, Simonson TM,

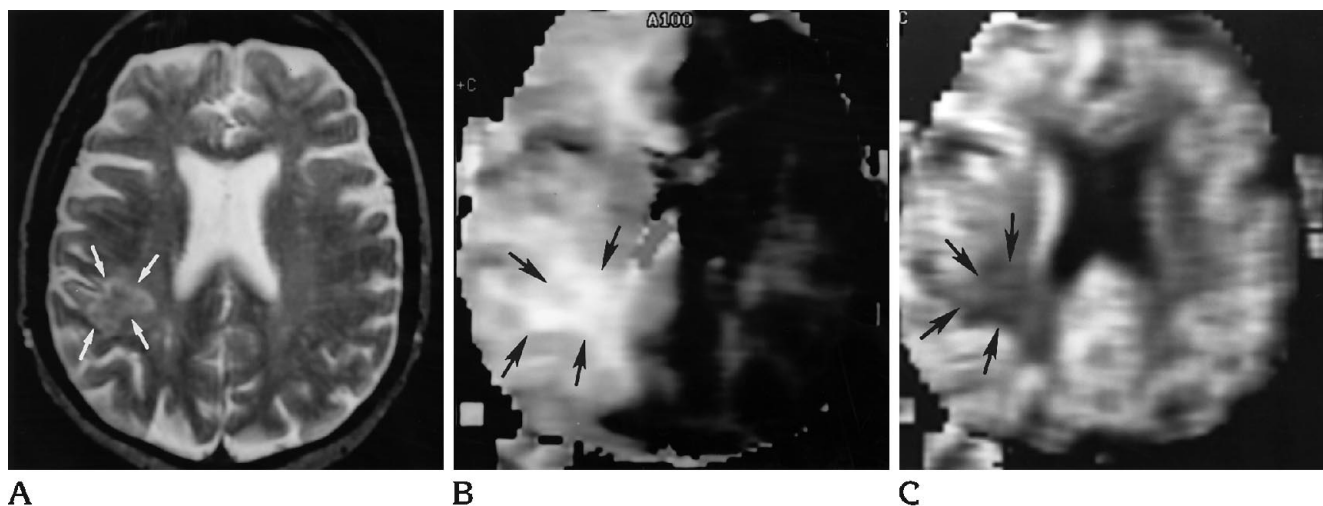


Fig 1. Differentiation between reversible and irreversible ischemic changes by perfusion imaging.

A, Axial T2-weighted image shows atrophic changes in this 84-year-old patient presenting with a transient ischemic attack. A subtle abnormality near the posterior watershed region (arrows) was not mentioned in the initial report.

B, Mean transit time map corresponding to A shows distinct hypoperfusion (bright) of the entire right hemisphere compared with normal perfusion of the left hemisphere (low signal intensity as a result of magnetic susceptibility effect). Note that the white matter has a higher signal intensity (lower perfusion) than that of the gray matter in both hemispheres. The least perfused area (the brightest area) of the right hemisphere is located in the watershed region (arrows).

C, Blood volume map corresponding to A shows relatively normal blood volume throughout the entire brain including the right hemisphere, despite clear evidence of hypoperfusion demonstrated by the mean transit time map shown in B. Note that the brain cortex has a much higher blood volume (bright) than that of the white matter (dark). The least perfused area demonstrated on the mean transit time map (B, arrows) also shows a decrease in blood volume (arrows). The area with severe hypoperfusion and low blood volume corresponds to the infarcted area on the T2-weighted image (A, arrows).

Zheng J, Ehrhardt JC, "Comparison of Echo-Planar Perfusion Imaging with Cerebral Angiography and T2-Weighted MR in the Evaluation of Transient Ischemic Attack," proceedings of the 33rd Annual Meeting of the American Society of Neuroradiology, Chicago, Ill, April 23-27, 1995:19) (Simonson TM, Yuh WTC, Crosby DL, et al, "Echo-Planar Diffusion and Perfusion Imaging of Ischemia in Patients without Significant Carotid Disease," proceedings of the 33rd Annual Meeting of the American Society of Neuroradiology, Chicago, Ill, April 23-27, 1995:23) (Fig 1). It is likely that there is variation in cellular toleration for prolonged ischemia between different individuals. For some, 15 minutes after the onset of symptoms may be too late for fibrinolysis treatment. For others, treatment several hours after the ideal 6-hour therapeutic window still may enable recovery (8). Therefore, the therapeutic window is unlikely to be a constant value for different individuals, even within the same species. A fixed 6-hour therapeutic window alone (and consider how hard it is among physicians to agree on 6 hours) may not always be optimal to determine when or when not to initiate fibrinolysis.

Jansen et al (13) report that early intervention also may increase the incidence of hemorrhagic complications. We have certainly seen hemorrhagic complications in patients with early intervention (within the first few hours). The cause remains to be determined. The risks associated with the administration of fibrinolytic agents in acute ischemic stroke are central and complex. The articles by del Zoppo et al (19) and Ferguson and Ferguson (18) addressed risk factors such as the underlying injury, fibrinolytic agents, dose rate, timing related to initial insults, vascular territory, and state of vasculature, as well as the risks associated with interventional procedures. The "underlying injury" likely reflects the state of tissue viability and reversibility (19). Reperfusion of necrotic tissue actually may worsen clinical outcome by aggravating edema and hemorrhage. Early reperfusion of nonviable and irreversibly damaged tissue using fibrinolytic agents, even though initiated soon after ischemic stroke, may do more harm than good. Therefore, information reflecting the state of viability and reversibility in ischemic tissue will not only im-

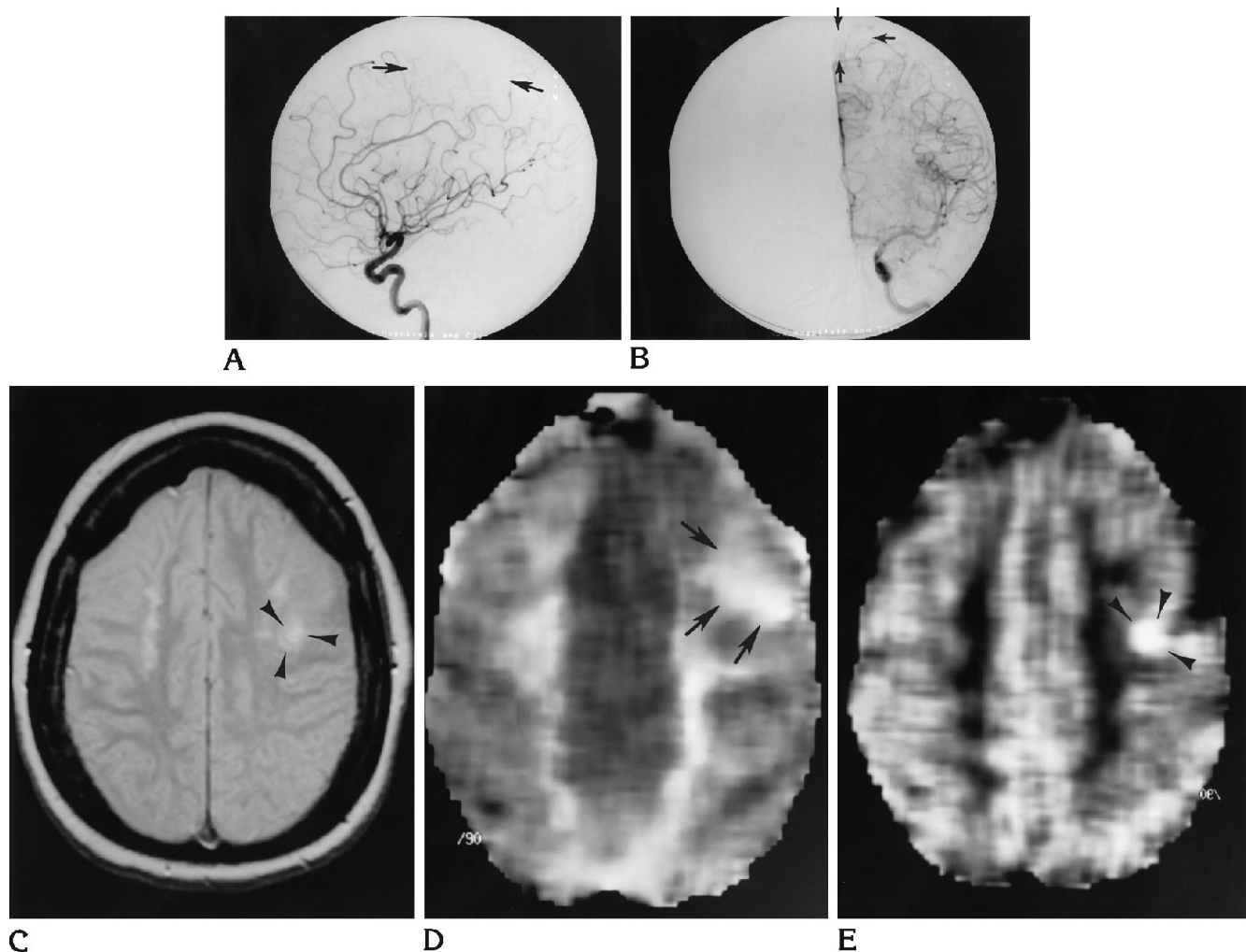


Fig 2. Microvascular collateral circulation demonstrated by perfusion imaging.

A and B, Angiogram shows area of relative avascularity (*between arrows*) in the anterior cerebral artery distribution in a patient with a history of multiple infarctions.

C, Axial proton-density image shows chronic ischemic changes in the watershed areas between the anterior cerebral arteries and middle cerebral arteries bilaterally. A subacute infarction (*arrowheads*) with intense contrast enhancement (not shown) also is noted. No parenchymal abnormality is found along the anterior cerebral artery distribution, including those areas with angiographic evidence of hypovascularity (A and B, *between arrows*).

D, Mean transit time map shows normal perfusion (*dark*) along the anterior cerebral artery territories bilaterally. Note areas with hypoperfusion (*bright*) along the watershed distribution between anterior cerebral artery and middle cerebral artery bilaterally. A wedge-shaped hyperperfusion area (*arrows*) in the left hemisphere also is noted. However, there is no corresponding abnormality on the proton-density image (C).

E, Blood volume map shows no evidence of decreased blood volume in the distribution of both anterior cerebral arteries. Multiple biopsies in the anterior cerebral artery distribution (normal proton density image, mean transit time, and regional cerebral blood flow map), including the relatively hypovascular area demonstrated by angiogram (A and B), showed normal brain tissue without evidence of ischemia. There is evidence of hyperemia (*arrowheads*) in the area of the subacute infarction (C, *arrowheads*). Normal blood volume is noted in the wedge-shaped hyperperfusion area (D, *arrows*), suggesting ischemic tissue without irreversible damage.

prove clinical outcome but also avoid complications.

Other important information such as cerebral blood flow, blood volume, lactic acidosis, pH, or water diffusion can be obtained only at the microscopic and/or cellular level (not gross anatomic level) and may not be provided by a con-

ventional angiogram. Macrovascular findings demonstrated on angiography such as complete proximal occlusion do not always correlate with the true blood supply of the ischemic tissue at a regional cellular level (Fig 2). In our daily practice, findings of complete occlusion of the proximal carotid artery in an asymptomatic

patient are not uncommon. The smallest vessels that can be demonstrated in a modern angiography suite at the present time are approximately 100 μm (21). We probably can evaluate adequately only those vessels greater than 300 μm . It is those vessels smaller than 100 μm (perhaps those smaller than 20 or 30 μm) that directly supply the target tissue. *The essential collateral circulation and regional blood supply provided by the microvasculature (<100 μm) cannot be adequately assessed by conventional angiography.*

In the past, it was not always possible to assess the viability and microvascular collateral circulation of the target tissue reliably and promptly, particularly in patients presenting with acute ischemic stroke. Functional imaging such as positron emission tomography, single-photon emission computed tomography, and xenon computed tomography may provide information related to tissue perfusion and blood volume. However, these techniques require long acquisition and processing times, which preclude their use in emergency situations. Recent advances in magnetic resonance (MR) imaging including spectroscopy and echo-planar imaging afford a prompt (imaging time is usually less than 30 minutes) and reliable means to obtain information that may affect cellular viability and reversibility.

MR Spectroscopy

The clinical application of MR spectroscopy in the evaluation of stroke patients has become a reality. In MR spectroscopy, metabolic changes frequently precede changes on conventional MR (22, 23). High lactate levels, found in the ischemic tissue during the acute stage of stroke, indicate a poor outcome (24) (Myers RE, Yamaguchi M, "Effects of Serum Glucose Concentration on Brain Response to Circulating Arrest," *J Neuropathol Exp Neurol* 1976;35:301 [Abstract]). *N*-acetyl-aspartate (NAA) is thought to be located in neurons (25). Decreased NAA concentrations may indicate neuronal loss or infarction. Increase in choline concentration may reflect membrane degeneration and demyelination. *Therefore, relatively low lactate levels and normal NAA and choline concentrations may indicate ischemic tissue that can be restored by appropriate therapy* (22). Single-voxel MR spectroscopy has been used to define the biochemical changes in

stroke. The important features, including the extent and severity of ischemia and the peripheral penumbra, can best be defined by MR spectroscopic imaging (Kugel H, Heindel W, Lanfermann H, Lackner K, "H¹ NMR Spectroscopic Imaging: Differentiation of Human Brain Tumors and Infarcts," proceedings of the 12th Annual Scientific Meeting of the Society of Magnetic Resonance in Medicine, August 14–20, 1993:1525) (van der Grond J, Balm R, Eikelboom BC, Mali WPTM, "H-1 MRSI of the Hypoperfused Brain," proceedings of the Second Meeting of the Society of Magnetic Resonance, August 6–12, 1994:611). In addition, MR spectroscopy can now estimate the region of ischemic (reversible) and infarcted brain more accurately than conventional MR (22). Very few MR spectroscopic studies have been performed within the 6-hour therapeutic window; several were done within 24 hours. More studies are needed for quantitative data to differentiate reversible and irreversible ischemic issues.

Diffusion MR

Diffusion imaging reflects abnormal water movement in the acute ischemic tissues caused by the failure of the high-energy Na-ATP pump. It permits the *in vivo* measurement of the tissue water apparent diffusion coefficient (26). In animal studies, reduced apparent diffusion coefficient indicates histologic evidence of cellular alterations (27). A measurable apparent diffusion coefficient is normal if there is no energy metabolism impairment, despite reduced blood flow. This method was reported to detect and delineate the ischemic area as early as 30 minutes after ischemic stroke in the animal model (28). In the earliest stage of ischemia, the high-signal areas shown by this method are possibly attributable to cytotoxic edema (28, 29), whereas the ischemic areas shown on diffusion-weighted images eventually develop infarction if left unprotected (28). Recently, diffusion MR has been used clinically to detect superacute stroke and has proved to be much faster and more sensitive in identifying ischemic areas than T2-weighted imaging (30). Although at the present time, there are no sufficient data to differentiate reversible from irreversible ischemic areas, evidence of early reperfusion in the ischemic tissue demonstrated by diffusion-weighted images can be essential in monitoring therapy. In the reperfusion ischemic model, reversibility

occurs more frequently in animals with evidence of early reperfusion (1 hour) demonstrated on diffusion-weighted images than in animals with late reperfusion (2 hours) (31).

Perfusion MR

Multisection perfusion images now can be acquired and processed within 5 minutes using echo-planar imaging technique (Crosby DL et al, "Comparison of Echo-Planar Perfusion Imaging," 1995) (Simonson et al, "Echo-Planar Diffusion," 1995). Unlike angiography, which permits the delineation of macrovascular anatomy, perfusion MR provides information related to microcirculation of the brain including mean transit time and regional cerebral blood volume maps (Figs 1 and 2). This method has been reported to be a powerful tool for the early detection of superacute ischemia (Crosby DL et al, "Comparison of Echo-Planar Perfusion Imaging," 1995) (Simonson et al, "Echo-Planar Diffusion," 1995) (34). Areas with perfusion deficit correlate well with those shown on diffusion MR images. Ischemic areas with severe hypoperfusion (little or no signal loss during the first pass of contrast agent) subsequently were found to be infarcted (32). The preliminary data of recent studies have suggested that ischemic tissues with prolonged mean transit time and marked decrease in relative regional cerebral blood volume tend to suffer irreversible damage, whereas infarction tends not to occur in tissues with intact regional cerebral blood volume (32) (Crosby DL et al, "Comparison of Echo-Planar Perfusion Imaging," 1995) (Simonson et al, "Echo-Planar Diffusion," 1995) (Warach S, Wielopolski P, Edelman RR, "Identification and Characterization of the Ischemic Penumbra of Acute Human Stroke using Echo-Planar Diffusion and Perfusion Imaging," proceedings of the 12th Annual Scientific Meeting of the Society of Magnetic Resonance in Medicine, August 14–20, 1993:249) (Figs 1 and 2). These findings appear to correlate with the underlying collateral circulation. With the echo-planar imaging technique, the acquisition and processing of diffusion and perfusion imaging can now be achieved within 12 minutes.

Finally, *the therapeutic window for stroke caused by venous occlusion (thrombosis) is somewhat different from that caused by arterial ischemia because of the differences in their underlying pathophysiologic processes: arterial*

*ischemia versus venous congestion (33, 34). In venous stroke (occlusion), the degree of ischemia is much less severe than in arterial ischemia (33). During the acute phases of venous occlusion, parenchymal enhancement is not seen, suggesting that the blood-brain barrier is intact because of the mild degree of ischemia. In the follow-up studies of 12 patients with venous stroke, focal infarction rarely was found (33). The abnormal parenchymal signal changes on T2-weighted images, which frequently resolved completely, are likely to represent pressure (venous)-driven interstitial edema rather than ischemic infarction. The authors pointed out that the actual damage inflicted on the brain tissue during venous occlusion is predominantly caused by venous congestion (hematoma, interstitial edema, and mass effect). Tsai et al (34) reported 18 cases of venous ischemia treated with endovascular urokinase (from 1 to 7 days after onset of symptoms; mean, 4 days). They correlated the abnormal MR findings (severity of interstitial edema, hemorrhage, and mass effect) with the degree of venous hypertension and clinical outcome. All patients with less than grade 3 MR abnormalities treated with endovascular fibrinolysis had recovered completely regardless of time of symptom onset. They concluded that *the extent of abnormal MR findings (radiologic window) instead of the time after onset of symptoms (therapeutic window in arterial ischemia) can be used to determine when or when not to initiate treatment.**

In conclusion, previous reports have suggested the potential benefit of fibrinolytic treatment in acute ischemic stroke but failed to provide convincing data to prove its efficacy. Many pitfalls and problems of previous studies have been addressed. We stress the importance of assessing the reversibility of the end organ, which has not been emphasized in previous reports and is limited by conventional imaging capabilities. With the advances in MR technology, we now may have the opportunity to evaluate the end organ in a prompt and reliable fashion. However, these new MR techniques still are in their infancy, and more quantitative data are needed to prove their value in differentiating reversibly and irreversibly damaged tissues. It is our belief that, in the foreseeable future, fibrinolysis therapy will be more successful when tissue viability/reversibility can be used routinely as adjunctive information to the therapeutic window in the treatment of acute ischemic

stroke. In contrast to patients with arterial ischemic stroke, those with venous stroke can be revived many hours beyond the 6-hour therapeutic window, and radiologic findings (radiologic window) appear to be more important than the therapeutic window in determining when or when not to initiate treatment and in predicting clinical outcome.

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