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Prethrombolysis Brain Imaging: Trends and Controversies

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Radiologists and clinicians agree that a patient with signs and symptoms of acute stroke may have a cerebral infarction whether or not imaging studies show it. If so, why routinely image all patients with acute stroke? The answer is that documenting hemorrhage precludes systemic anticoagulation, and that in approximately 10% of all stroke patients the symptoms result from causes other than ischemia (eg, vascular malformations or tumors). If results of an initial computed tomographic (CT) study of the brain are normal and the symptoms resolve within 24 hours of onset, a patient is generally assumed to have had a transient ischemic attack (TIA). If the symptoms remain fixed or increase during that time, an infarction has occurred and a follow-up CT study of the brain may be done to document it or to exclude a hemorrhage (particularly if the symptoms worsen). During the past few years, this "traditional" work-up for patients with acute stroke has been challenged, owing to the pursuit of aggressive therapies aimed at reestablishing blood flow, reducing the size of the infarction, and protecting the surrounding brain that is at risk (ischemic penumbra). Because the window of opportunity for thrombolytic therapy is short (generally 1 to 5 hours), we can no longer wait 24 hours to determine whether a patient has had a TIA or an infarction. Since this differentiation is not always possible on the basis of early physical examination, the burden of proof has fallen upon imaging studies. In this article, I review the different imaging techniques that have historically been used to examine patients with acute stroke and the techniques that have recently been developed or that are currently under development.

The first technique that provided information regarding the condition of the intracranial vessels in patients with acute stroke was catheter angiography. Recently, because some investigators consider intraarterial thrombolysis an excellent method for treating acute cerebral infarctions, angiography has been regaining its importance in the evaluation of acute stroke (this issue is addressed later). Approximately 30 years ago, two large series reviewed the complications of cerebral angiography (1, 2). The overall morbidity rate at that time was 2.5% and the mortality rate was 0.5%; and it was noted that the rate of complications had increased fourfold in patients with cerebrovascular disease (3) owing to problems resulting from catheter manipulation and the injection of irritating contrast material. These observations since led to a conservative use of angiography in this setting. Children constitute the only group of acute stroke patients for whom angiography is still advocated, although magnetic resonance (MR) angiography is now thought to be sufficient (4). Since the majority of cerebral infarctions are embolic in nature, an angiographic diagnosis is based on finding an occluded artery. This abnormality is time dependent, because clots may disappear rapidly, a fact noted by early angiographers (5, 6). Therefore, a cerebral infarction may be present even in the absence of an obstructed artery. Because of the technical difficulties associated with angiography and its inherent morbidity, the 1960s saw the development of some noninvasive imaging techniques for acute stroke patients. These included thermography, phonoangiography, radionuclide brain scanning, and Doppler sonography (3). The first two techniques have disappeared completely. Radionuclide brain scanning was popular before the advent of CT and is used today only in selected patients. Doppler sonography is useful in evaluating the extracranial internal carotid artery predominantly as a screening method for atherosclerosis.

In the 1970s, CT revolutionized brain imaging. Because of the poor resolution provided by the early units, CT could not show acute infarctions. Early experience revealed that

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CT showed only 50% of infarctions during the first 48 hours (3). It was also noted that contrast administration increased the conspicuity of subacute but not of acute infarctions (7). Although, currently, CT may show findings as early as 3 to 6 hours after ictus, it is still accepted that its overall sensitivity is poor during the hyperacute (initial 24-hour) period (8, 9). Thus, CT is not able to distinguish between TIAs and early infarctions. Administration of contrast material is not indicated in the hyperacute period because it is well documented that at least 24 hours are required for enhancement to occur (10). In addition, there is controversy surrounding the presumed toxicity of contrast material to the already damaged brain. Contrast administration is indicated when plain CT findings suggest an underlying cause other than ischemia for a patient's symptoms. Because of its availability and straightforward interpretation, CT continues to be used in most patients with acute stroke. Two well-known recent textbooks on emergency and internal medicine state that the presence of large infarctions precludes thrombolytic therapy or heparinization (11, 12). The definition of a large infarction is, unfortunately, not given.

Curiously, heparinization, which is the traditional method of treating acute stroke, has never undergone the rigorous evaluation to which the newer drugs are being submitted. CT scanning of a patient with acute stroke who is a candidate for thrombolytic therapy is not without a few demands. At my institution, selected stroke patients undergo early systemic administration of alteplase. This means that all patients who are within the therapeutic window (0 to 3 hours) need to be scanned immediately. This problem is partially solved by having a CT unit in the emergency department. Requisitions are red stamped as requiring a "stat CT" and priority is given to these patients. The studies are interpreted as they are being obtained, and findings are promptly relayed to the emergency department physician. Contraindications for this type of treatment are straightforward (hemorrhage and mass effect with midline shift), with the exception of one: parenchymal hypodensity and/or effacement of sulci in more than 33% of the middle cerebral artery (MCA) territory. Because of the variable extension of the vascular territories in the brain, a reliable and consistent assessment of this extension may be difficult. The success of alteplase therapy is dependent on the time of its administration; that is, patients started on alteplase within 90 minutes of the ictus tend to have early recanalization and a better prognosis. In some alteplase therapy series, only CT was obtained (no angiography), meaning that some successfully treated patients probably had TIAs and not true infarctions, which would have skewed these series toward good results.

Regardless of these observations, it is my opinion that CT will continue to be a mainstay in the imaging of patients with acute stroke. Indeed, newer applications of CT, such as functional CT and CT angiography, may increase its use. Spiral CT data may be acquired before and after the administration of contrast material to assess whole-brain cerebral blood flow (13) (Fig 1). Additionally, these data may be used to produce whole-brain angiograms (Fig 2).

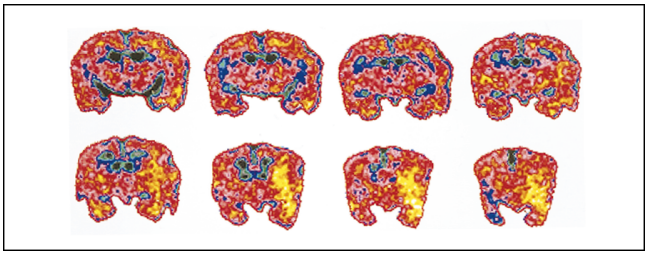


Fig 1. Cerebral blood volume measurement with functional CT in vitro. Coronal contiguous absolute blood volume maps (1-mm section thickness) obtained in an animal model measured with a subtraction 3-D function CT technique and after the administration of iodinated contrast material. *Yellow* indicates areas of low blood volume corresponding to a region of ischemia that developed within 3 hours of MCA occlusion (from Hamberg et al [13].)

It is possible that functional CT will prove to be a cost-effective, rapid, and simple method for the evaluation of acute stroke (13). CT is not only important for initial diagnosis but may also help in predicting the outcome of patients undergoing thrombolytic therapy. In one alteplase study, it was found that large infarctions tended to develop in patients with early signs of ischemia and a hyperdense MCA by CT (14). Additionally, CT is helpful during or after completion of alteplase therapy because up to one third of patients will incur hemorrhage (14, 15). Clinically evident neurologic worsening is seen, however, in less than 10% of these patients (15). The addition of xenon to CT also may help in determining acute infarctions, even immediately after presentation. This technique requires a special system for the delivery of the gas and approximately 20 minutes to administer the dose, obtain the study, and transfer the data. Moreover, in order to calculate cerebral blood flow maps, these data need to be evaluated on an offline computer. For these reasons, this technique is not widely available.

The portability and low cost of sonographic equipment would make this method ideal for examining patients with acute stroke. Indeed, Doppler sonography has been used for evaluation of arterial patency following acute stroke (16–18). Although this technique can depict only the proximal vessels in the circle of Willis, one study showed that 70% of patients with cerebral infarctions had abnormal flow patterns in a proximal MCA while no patients with TIAs had such findings (16). Sonography may therefore play a role in the diagnosis of acute stroke. Unfortunately, sonography is operator dependent and time consuming. In addition, neither sonography nor CT is able to detect distal vessel occlusion. There is evidence that with systemic thrombolysis, distal occlusions will recanalize more often and faster than proximal occlusions. The sensitivity of transcranial Doppler sonography may be increased by combining it with other techniques. In one study, the combination of transcranial Doppler sonography and single-photon emission CT (SPECT) was able to target smaller infarctions (which are the ones that respond better to thrombolysis). By itself, SPECT may also be useful in the

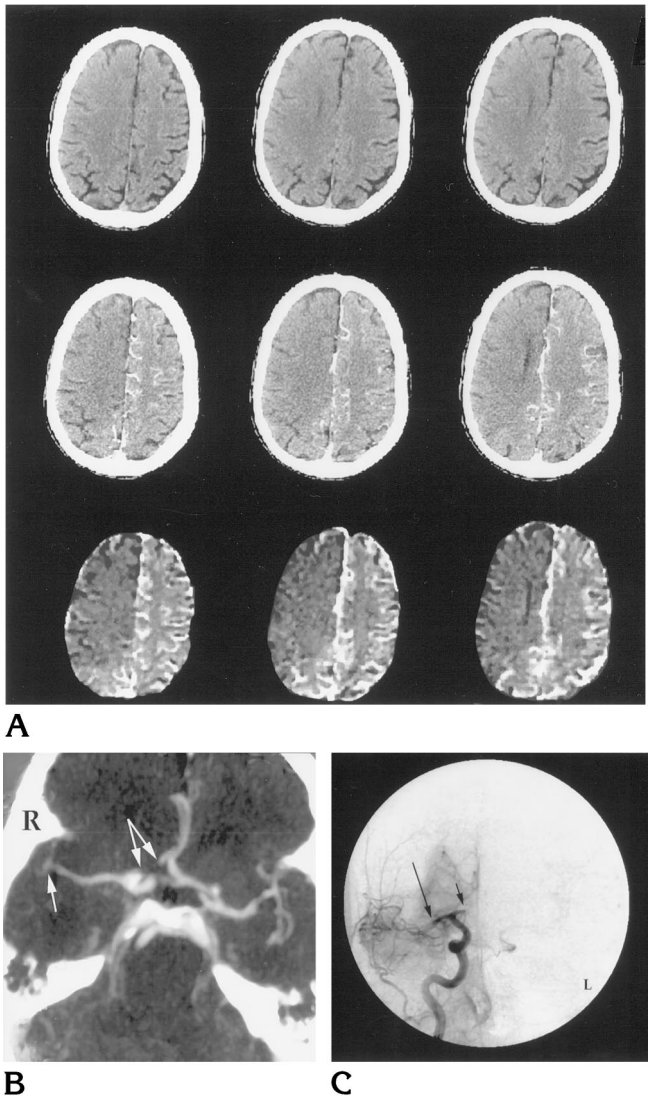


Fig 2. Cerebral blood volume measurement with functional CT in vivo.

A, Axial noncontrast CT scans (*top row*) show subtle effacement of cortical sulci on the right side. On the corresponding postcontrast scans (*middle row*), intravascular enhancement is present on the left but not on the right side. Subtraction of both images (*bottom row*) shows decreased attenuation on most of the right side.

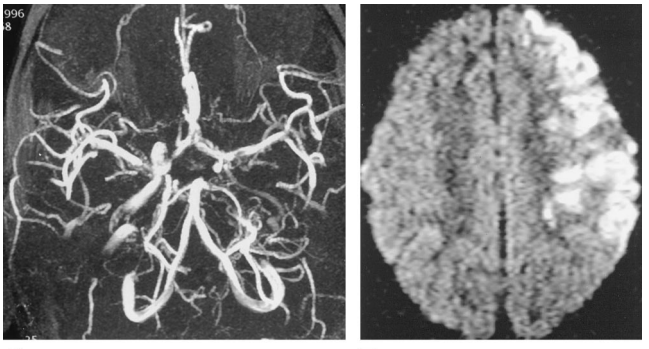
B, Collapsed multiprojection volume-reconstructed CT angiogram from the same patient shows lack of homogeneous opacification in the right A1 segment (*double arrows*) of the anterior cerebral artery (ACA) and at the bifurcation (*single arrow*) and M2 segment of the right MCA.

C, Coronal projection from a catheter angiogram during injection of the right internal carotid artery shows cutoffs in the ACA (*short arrow*) and MCA (*long arrow*) (courtesy of L. Hamberg).

evaluation of acute stroke (19). SPECT is able to provide some prognostic information in patients with acute stroke. In one study, a marked reduction in residual cerebral blood flow in a region of acute ischemic infarction signified an increased risk for hemorrhagic transformation (20). Because strokes tend to occur at odd hours, SPECT may not be readily available in all institutions.

MR imaging is the single technique that provides the most information regarding acute cerebral infarctions. MR imaging can reveal gross morphology, information regarding the restriction of movement of water at the molecular level (diffusion-weighted imaging), alterations in metabolites (MR spectroscopy), and status of the vasculature (MR angiography). Studies comparing the sensitivity of MR imaging versus CT for the detection of acute infarction clearly show the superiority of the former (9, 21). On noncontrast MR imaging studies, the initial signs of infarction include the absence of arterial flow void and increased signal intensity in the cortex, particularly on proton density–weighted images (22). The first sign is seen immediately after the ictus and the second one during the initial 8 hours after the ictus. The addition of contrast material results in intravascular enhancement, which makes an occluded or nearly occluded artery much more visible (23). Intravascular enhancement may be seen 2 to 4 hours after the ictus. MR angiography clearly displays occluded vessels in the hyperacute period (24, 25) (Fig 3A). Unfortunately, the ability to reliably evaluate distal vessels by MR angiography is limited, and because many of these patients are unstable, motion may degrade the images. MR spectroscopy with the use of proton and phosphorus metabolites also provides helpful information regarding acute strokes. Phosphorus MR spectroscopy shows changes in high-energy phosphate metabolism, with acute cerebral infarctions showing elevation of inorganic phosphorus and decreased adenosine triphosphate (26). Because phosphorus MR spectroscopy necessitates a head coil that is tuned to the resonant frequency of that metabolite, it is less popular than proton MR spectroscopy, which may be performed with existing head coils. Proton MR spectroscopy shows that acute infarctions contain elevated lactate and reduced *N*-acetylaspartate, choline, and creatine (27). The ischemic penumbra may show lactate but normal concentrations of other metabolites. These findings may indicate that such regions have a better chance of recovery. Unfortunately, MR spectroscopy is motion sensitive and even in the most experienced hands it requires at least 10 minutes. In addition, MR spectroscopy is not available in all units, as the manufacturers generally charge approximately 10% of the value of the unit for the spectroscopic package. Last, interpretation of MR spectra requires experience that very few radiologists possess.

Diffusion-weighted MR imaging is a relatively new technique that allows for visibility of impaired random motion of water molecules within infarctions. The term *infarction* derives from the Latin, meaning "to stuff in." The *infarcted zone* is edematous (stuffed with water) and restricts the random water motion. By applying a diffusion-sensitizing gradient, these abnormal zones are seen as increased sig-



A B

Fig 3. MR imaging in hyperacute infarction.

A, Collapsed view from 3-D time-of-flight MR angiogram in a child with onset of right hemiplegia only minutes before arriving in the emergency department. The left internal carotid artery is not visible and the branches and intensity of flow-related enhancement in the left MCA are decreased.

B, Axial 6-mm-thick diffusion-weighted image (B = 1000, high-strength gradient) shows hyperintensity in left frontoparietal cortex, extending into underlying white matter. This hyperintensity is related to restriction of the random motion of water molecules and consistent with acute infarction.

nal intensity (Fig 3B). Diffusion-weighted MR imaging can show an infarction minutes from its onset and is probably the most sensitive diagnostic technique available for the evaluation of acute stroke. The entire brain is imaged in 4 to 5 seconds; therefore, we obtain diffusion-weighted images in all stroke patients. These images are also very helpful when evaluating an acute infarction superimposed upon an older one. If diffusion-weighted images are obtained at the beginning of an MR study and are positive, they may obviate contrast administration. Our neurologists like these images because they provide important information and are easily interpreted. A drawback of this technique is the high cost of the equipment. To perform diffusion-weighted imaging, an MR unit needs to be echo-planar capable. MR imaging may also be used to obtain dynamic and real-time cerebral blood flow maps after contrast administration but, unfortunately, this technique has not gained popularity.

From the above discussion it seems logical to assume that MR imaging is the best single imaging technique for evaluation of acute stroke. It should not be forgotten that MR imaging lacks some sensitivity in the detection of acute hemorrhage (particularly at field strengths less than 1.5 T) and that studies in patients with acute stroke need to include sequences, such as gradient-echo images, that are inherently sensitive to fresh blood products.

And so we now come back to catheter angiography. In the neuroradiologic community, there is a consensus that many patients with acute infarction may benefit from intraarterial thrombolysis (28). Because the Food and Drug Administration has approved systemic alteplase therapy for acute cerebral infarction, the enthusiasm for catheter-directed thrombolysis has decreased (at least from our clinical colleagues). Although intraarterial thrombolysis has been successfully used in all major intracranial territories, published series suffer from being small and heterogeneous in their selection of patients and drugs. Adequate intraarterial therapy requires the use of microcatheters placed beyond or in the clot. Administration of thrombolytic agents is time consuming, generally in the range of 60 to 120 minutes (29). Therefore, intraarterial thrombolysis is not widely applicable, is skill dependent, and probably will continue to be restricted to a few specialized centers. These issues are further complicated by the risk of hemorrhage and by the fact that vessel recanalization may not be an adequate marker for improved prognosis (28). That is, some patients with complete recanalization will not show improvement of symptoms while some patients with no recanalization have nearly complete resolution of motor deficits (about one third of all patients with cerebral infarctions will show some improvement regardless of the therapy they received). Perhaps the only instances in which heroic measures at lysing a clot may be attempted are in those patients with hyperacute occlusion of the vertebrobasilar system. In these patients, the prognosis is poor and intraarterial thrombolysis is often the only resort available.

In summary, stroke is common and results in a significant financial expenditure. The ideal screening imaging technique should be capable of differentiating hyperacute cerebral infarctions from TIAs. Noncontrast CT is the most widely used study for evaluating acute stroke, and new applications will ensure its continued use. In my opinion, the information provided by CT in the hyperacute period is limited to the presence or absence of hemorrhage, and I believe that MR imaging serves us better. Ideally, diffusion-weighted MR imaging should be initially done in all patients with acute stroke. Because of its inherent sensitivity to magnetic susceptibility artifacts, it shows hemorrhage readily and also clearly outlines the infarcted territory. Vascular anatomy may be depicted with MR angiography of the carotid bifurcation in the neck and of the circle of Willis. In our MR units, we are able to obtain the above-mentioned sequences in approximately 15 minutes. If findings on the diffusion-weighted images are normal, we perform a contrast-enhanced MR study of the brain.

References

1. Lyons C. Progress report of the joint study of extracranial arterial occlusion. In: Millikan CH, Siekert RG, Whisnant JP, eds. *Cerebral Vascular Diseases, 4th Conference*. New York, NY: Grune & Stratton; 1965
2. Fields WS. Progress report of the joint study on extracranial arterial occlusion. In: Millikan CH, Siekert RG, Whisnant JP, eds. *Cerebral Vascular Diseases, 5th Conference*. New York, NY: Grune & Stratton; 1966
3. Taveras JM, Wood EH. Cerebral angiography. In: Taveras JM, Wood EH, eds. *Diagnostic Neuroradiology*. 2nd ed. Baltimore, Md: Williams & Wilkins; 1976:857–909
4. Ball WS. Cerebrovascular occlusive disease in childhood. *Neuroimaging Clin N Am* 1994;4:393–421
5. Gannon WE, Chait A. Occlusion of middle cerebral artery with recanalization. *AJR Am J Roentgenol* 1962;88:24

6. Allock JM. Occlusion of the middle cerebral artery: serial angiography as a guide to conservative therapy. *J Neurosurg* 1967;27: 353
7. Davis KR, Taveras JM, New PFJ, Schnur JA, Robertson GH. Cerebral infarction diagnosis by computerized tomography: analysis and evaluation of findings. *AJR Am J Roentgenol* 1975;124: 643
8. Inoue Y, Takemoto K, Miyamoto T, et al. Sequential computed tomography scans in acute cerebral infarct. *Radiology* 1980;135: 655–662
9. Weingarten K. Computed tomography of cerebral infarction. *Neuroimaging Clin N Am* 1992;2:409–419
10. Kuroiwa T, Sedia M, Tomida S, et al. Discrepancies among CT, histological, and blood-brain barrier findings in early cerebral ischemia. *J Neurosurg* 1986;65:199–202
11. Kothari RV, Borsan W. Management of stroke. In: Tintinalli JE, Ruiz E, Korme RI, eds. *Emergency Medicine*. 4th ed. New York, NY: McGraw Hill; 1996:1014–1020
12. Kistler JP, Ropper AH, Martin JB. Cerebrovascular disease. In: Isselbacher RJ, Braunwald E, Wison JD, et al, eds. *Harrison's Principles of Internal Medicine*. 13th ed. New York, NY: McGraw Hill; 2233–2255
13. Hamberg LM, Hunter GJ, Kierstead D, Lo EH, González RG, Wolf GL. Measurement of cerebral blood volume with subtraction three-dimensional functional CT. *AJNR Am J Neuroradiol* 1996; 17:1861–1869
14. Wolper SM, Bruckmann H, Greenlee R, et al. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. *AJNR Am J Neuroradiol* 1993;14: 3–13
15. Del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol* 1992;32:78–86
16. Alexandrov AV, Bladin CF, Norris JW. Intracranial blood flow velocities in acute ischemic stroke. *Stroke* 1994;25:1378–1383
17. Alexandrov AV, Bladin CF, Eherlich Lem Norris JW. Noninvasive assessment of intracranial perfusion in acute cerebral ischemia. *J Neuroimaging* 1995;5:76–82
18. Grosset D, Lees M. Application of transcranial Doppler sonography in acute ischemic stroke. *Stroke* 1992;23:1840–1841
19. Hanson SK, Grotta JC, Rhoades H, et al. Value of single-photon emission tomography in acute stroke therapeutic trials. *Stroke* 1993;24:1322–1329
20. Ueda T, Hatakeyama T, Kumon Y, Sakaki S, Uraoka T. Evaluation of risk of hemorrhagic transformation in local intra-arterial thrombolysis in acute ischemic stroke by initial SPECT. *Stroke* 1994;25:298–303
21. Bryan RN, Levy LM, Whitlow WD, et al. Diagnosis of acute cerebral infarction: comparison of CT and MR imaging. *AJNR Am J Neuroradiol* 1991;12:611–620
22. Yuh WTC, Crain MR, Loes DJ, et al. MR imaging of cerebral ischemia: findings in the first 24 hours. *AJNR Am J Neuroradiol* 1991;12:621–629
23. Elster AD, Moody DM. Early cerebral infarction: gadopentetate dimeglumine enhancement. *Radiology* 1990;177:627–632
24. Mathews VP, Barker PB, Bryan RN. Magnetic resonance evaluation of stroke. *Magn Reson Q* 1992;8:245–263
25. Maas K, Barkovich AJ, Dong L, Edwards MS, Piecuch RE, Charlton V. Selected indications for and applications of magnetic resonance angiography in children. *Pediatr Neurosurg* 1994;20: 113–125
26. Levine SR, Helpern JA, Welch KMA, et al. Human focal cerebral ischemia: evaluation of brain pH and energy metabolism with P-31 NMR spectroscopy. *Radiology* 1992;185:537–544
27. Mathews VP, Barker PB, Blackband SJ, Chatham JC, Bryan RN. Cerebral metabolites in patients with acute and subacute strokes: concentrations determined by quantitative proton MR spectroscopy. *AJR Am J Roentgenol* 1995;165:633–638
28. Ferguson RDG, Ferguson JG. Cerebral intraarterial fibrinolysis at the crossroad: is a phase III trial advisable at this time? *AJNR Am J Neuroradiol* 1994;15:1201–1216
29. Zeumer H, Freitag HJ, Zanella F, Thie A, Arning C. Local intraarterial fibrinolytic therapy in patients with stroke: urokinase versus recombinant tissue plasminogen activator (r-TPA). *Neuroradiology* 1993;35:159–162