Background: Intravenous thrombolysis for acute ischemic stroke has been investigated in several clinical trials without enough information on collateral blood flow and perfusion deficit in the ischemic areas. The therapeutic time window varies from patient to patient depending on these factors. Triphasic perfusion computed tomography (TPCT) can provide this information as reliably as conventional angiography.

Objective: To assess the safety and efficacy of thrombolysis within 3 or 7 hours of stroke onset according to the extent of perfusion deficit on TPCT.

Methods: In 46 patients with acute middle cerebral artery (MCA) territory stroke, TPCT was performed with power injector–controlled, intravenous administration of contrast media after taking precontrast CT scans. Sequential scans of early, middle, and late phases were performed. The entire procedure took 5 minutes. Depending on collateral blood flow, the perfusion deficit on TPCT was graded as “severe perfusion deficit” or “moderate perfusion deficit.” Twenty-nine patients were excluded based on clinical, laboratory, and TPCT findings. Seventeen patients were treated with an intravenous recombinant tissue-type plasminogen activator, 0.9 mg/kg. The 17 treated patients were divided into 2 groups: group 1 with small severe perfusion deficit (>33% but ≤50% of the presumed MCA territory) and group 2 with medium-sized severe perfusion deficit (>33% but ≤50% of the presumed MCA territory). The 13 patients in group 1 were treated within 7 hours of onset and the 4 patients in group 2 were treated within 3 hours.

Results: Initial mean National Institutes of Health Stroke Scale score was 12.1 (range, 6.0-20.0) in group 1 and 19.0 (range, 18.0-21.0) in group 2. The initial score correlated better with the total extent of moderate perfusion deficit and severe perfusion deficit than that of severe perfusion deficit alone. Mean time lapse to thrombolysis was 4.2 hours (range, 1.5-7.0 hours) in group 1 and 2.2 hours (range, 1.9-2.5 hours) in group 2. Eight patients (47%), 7 from group 1 and 1 from group 2, improved by 4 points or more from baseline Stroke Scale score within 24 hours of thrombolysis. Patients with moderate perfusion deficit of 50% or more of MCA territory (n=4) had a better chance of early improvement than did those (n=13) with moderate perfusion deficit of less than 50% (4 of 4 vs 4 of 13). No fatal hemorrhage occurred. Only 1 patient (6%) had symptomatic small basal ganglia hemorrhage after thrombolysis.

Conclusions: Thrombolysis can be safely performed within 3 or 7 hours of stroke onset according to the extent of severe perfusion deficit on TPCT. A larger extent of moderate perfusion deficit on TPCT may predict early improvement after thrombolysis.

From the Departments of Neurology (Drs K. H. Lee, S. J. Lee, Cho, Kim, Song, and Chung and Ms Jin) and Radiology (Drs Na and Byun), Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

Computed tomography (CT) is widely used in patients with acute ischemic stroke to exclude acute hemorrhage or other diseases mimicking ischemia (tumor and subdural hematoma) when antithrombotic therapy is considered. Perfusion deficit and collateral blood flow are the important factors associated with the safety and efficacy of thrombolytic therapy for acute middle cerebral artery (MCA) stroke.1,2 The risk of hemorrhagic transformation after recanalization of the occluded arteries by thrombolytic therapy is considered high when pretherapeutic residual cerebral blood flow is markedly reduced.3 However, precontrast CT cannot provide enough information about perfusion deficit and collateral circulation.

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Conventional angiography can assess the extent of perfusion deficit and collateral blood supply in patients who undergo intra-arterial thrombolysis.1 Functional imaging modalities such as positron emission tomography, single-photon emission CT, xenon CT, and perfusion magnetic resonance imaging (MRI) can provide information about regional cerebral blood flow.6,7 But, these tests take hours to perform in ad-
PATIENTS AND METHODS

We prospectively screened 46 patients with acute ischemic stroke in the MCA territory who arrived within 6 hours of onset at the emergency department of a tertiary care hospital in Seoul, Korea, between September 1997 and October 1998. The human ethics committee of the hospital approved the study. Inclusion criteria for the study were (1) clinical diagnosis of acute MCA stroke within 7 hours of symptom onset; (2) a minimum NIHSS score of 4, except for isolated aphasia or isolated hemianopsia; and (3) informed consent from the patient or his/her relatives. Exclusion criteria included (1) uncompensated hypertension (blood pressure >185/110 mm Hg), (2) hematologic disease or bleeding diathesis, (3) oral anticoagulation therapy with an international normalized ratio greater than 1.7, and (4) evidence of intracranial hemorrhage on precontrast CT. We also excluded those with uncertain symptom onset and those who were already improving. Triphasic perfusion CT was performed only in patients with a normal serum creatinine level (>124 μmol/L [=1.4 mg/dL]). It took 20 minutes to get the level of serum creatinine after blood sampling. The baseline NIHSS score was obtained from each patient during the process.

IMAGING TECHNIQUES

A brain TPCT protocol was developed using a helical CT scanner (High-speed Advantage GE Medical Systems, Milwaukee, Wis) by one of us (D.G.N.), which is described in detail elsewhere.10 After precontrast CT imaging of the whole brain, contrast-enhanced TPCT was performed in all patients. Ninety milliliters of 68% nonionic contrast material (Optiray 320; Mallinckrodt Medical, Quebec, Quebec) was administered by a power injector into an antecubital vein (18-gauge intravenous cannula) at a rate of 3 mL/s. Then, early-, middle-, and late-phase images were obtained with scan delays of 18, 30, and 80 seconds, respectively. Scanning began from the level of 1 cm below the caudal proximal MCA identified on precontrast CT and continued toward the vertex. Six slices of images were obtained at the early phase and 10 slices of images were obtained at each of the middle and late phases. All images of unenhanced and enhanced CT were obtained with 10-mm collimation and at a 10-mm/s table speed, and the images were reconstructed at 3-mm intervals. The total scanning time for the completion of 3 acquisitions was 90 seconds, and the total time for scanning (1 second per slice) and reconstruction of images (3 or 4 seconds per image) was less than 3 minutes.

IMAGE INTERPRETATION

Two neuroradiologists (D.G.N. and H.S.B.) read the precontrast CT and TPCT scans without information on the NIHSS score of each patient. The interpreters determined the presence of early CT signs of ischemia, such as hypodense MCA sign, attenuation of the lentiform nuclei, loss of the insular ribbon, or hemispheric sulcal effacement, on precontrast CT. The interpreters determined the presence of the MCA (stem or bifurcation) occlusion with hypodense MCA sign on precontrast CT and nonenhancing MCA segment on the early- and middle-phase images of TPCT.

The perfusion deficit on TPCT was defined as decreased arterial enhancement on the early-phase images, poor perfusion areas on the middle- and late-phase images, and delayed arterial enhancement on the late-phase images. The perfusion deficit was graded as severe if the ischemic zone of the affected MCA territory was shown as decreased attenuation relative to contralateral normal parenchyma with little or no collateral blood flow on the early-, middle-, and late-phase images by visual inspection and moderate if the ischemic zone of the affected MCA territory was shown as (1) decreased attenuation on the early-phase images and normal attenuation with markedly slow collateral blood flow on the middle- and late-phase images or (2) decreased attenuation on the early- and middle-phase images and normal on the late-phase images. The extent of severe perfusion deficit and moderate perfusion deficit was estimated as an approximate percentage of the presumed MCA territory using 3 categories: 33% or less (small), more than 33% but 50% or less (medium sized), and more than 50% (large). We were careful to estimate the extent of severe perfusion deficit in the lower division territory of the MCA because of CT artifact in the inferior and middle temporal lobes.

TREATMENT

Of 46 patients screened for entry, 17 satisfied all clinical and CT entry criteria. Of 29 patients excluded, 5 had spontaneous recovery, 6 refused thrombolytic therapy, 8 with ICA or proximal MCA occlusion had a large severe perfusion deficit (>50% of the presumed MCA territory), 4 with medium-sized severe perfusion deficit (>33% but ≤50 of the presumed MCA territory) were too late to start treatment within 3 hours of onset, and 6 were excluded for other reasons. The remaining 17 patients received intravenous rtPA, 0.9 mg/kg (alteplase, maximum of 90 mg), by infusing 10% as a bolus followed by constant infusion of the remaining 90% for 60 minutes. All 17 treated patients were divided into 2 groups: group 1 with small severe perfusion deficit (≤33% of the presumed MCA territory) and group 2 with medium-sized severe perfusion deficit. The 13 patients in group 1 were treated within 7 hours of onset and the 4 patients in group 2 were treated within 3 hours. We followed up the patients with NIHSS scores before and after thrombolysis and on the first, third, and seventh day and with the modified Rankin scale 3 months after the onset of stroke. Follow-up diffusion imaging was performed in 15 patients within 24 hours of the initial TPCT.
thrombolytic treatment increased the chance of good outcome in patients with a small hypoattenuating area (≤33% of the presumed MCA territory). However, rtPA therapy had no beneficial effect but increased the risk for fatal brain hemorrhage in patients with normal CT scans and a large hypoattenuating area (>33% of the presumed MCA territory). Moreover, hypodensity covering more than 50% of the MCA territory had an 85% positive predictive value for fatal clinical outcome after thrombolysis within 6 hours.17

Figure 1. Patient 2 with small severe perfusion deficit and large moderate perfusion deficit. A, Low density in the right medial temporal lobe and the posterior limb of the internal capsule (arrows) on precontrast computed tomography (CT). B, Early-phase images of triphasic perfusion CT show decreased vascular enhancement and hypoattenuating areas in the right middle cerebral artery territory compared with the left side. C, Middle-phase images show a change of hypoattenuating areas to isodense areas (moderate perfusion deficit) with delayed collateral blood flow. D, Late-phase images show delayed, asymmetric vascular enhancement in the temporal cortex and persistent hypoattenuating areas in the posterior limb of the right internal capsule and the medial temporal lobe. Arrows indicate severe perfusion deficit. E, Diffusion-weighted magnetic resonance imaging performed immediately after thrombolysis shows the ischemic lesions in the zone of severe perfusion deficit (medial temporal lobe and posterior limb of internal capsule). F, Follow-up magnetic resonance imaging 5 days after stroke onset shows infarction involving the right anterior choroidal artery territory (medial temporal lobe, posterior limb of internal capsule, and thalamus) and insula. G-I, Nonenhancing segments (arrowheads) of the right distal internal carotid artery (ICA) could be identified on the early-phase images compared with the normal left ICA (arrows) by adjusting windows of CT images. J, Absent flow signal in the right distal ICA on magnetic resonance angiography, which was obtained immediately after thrombolysis.
Triphasic perfusion CT (TPCT) is as reliable as conventional angiography for the evaluation of occlusion of the proximal MCA, collateral blood supply, and the extent of perfusion deficit within the first hours of acute MCA territory stroke. \(^{18}\) We\(^{16,20}\) reported the usefulness of perfusion deficit within the first hours of acute ischemic stroke. Treatment strategies can be individualized depending on the extent of severe perfusion deficit. 

RESULTS

Data from the 17 treated patients are summarized in Table 1. The initial precontrast CT showed early signs of ischemia (loss of insular ribbon, attenuation of lenticulostriate arteries, and loss of gray-white matter distinction)
in 11 patients. However, the initial TPCT revealed the extent of perfusion deficit and delayed collateral circulation more clearly than did precontrast CT in all patients except patient 12, who had a small striatocapsular infarct. The initial NIHSS score correlated better with the total extent of severe perfusion deficit and moderate perfusion deficit than that of severe perfusion deficit alone. The mean time interval between symptom onset and thrombolysis was 4.2 hours (range, 1.5-7.0 hours) in group 1 and 2.2 hours (range, 1.9-2.5 hours) in group 2. Mean NIHSS score before thrombolysis was 12.1 (range, 6.0-20.0) in group 1 and 19.0 (range, 18.0-21.0) in group 2. Eight patients (47%), 7 from group 1 (patients 1, 2, 3, 4, 6, 8, and 13) and 1 from group 2 (patient 14), improved by 4 points or more from the baseline NIHSS score within 24 hours. The hypoattenuating areas on precontrast CT and lesions on diffusion imaging performed within a day after the initial TPCT were confined to the zone of severe perfusion deficit on TPCT (Figure 1). These areas did not recover completely on the follow-up CT or MRI. Four

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<th>Table 2. Correlation of Clinical Outcome With Perfusion Deficit, Time Lapse, and Striatocapsular Involvement*</th>
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<th>Favorable Outcome (n = 13)†</th>
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*Data are given as number of patients with clinical outcome per total number of patients.
†Four patients (patients 1, 2, 5, and 10) were lost during 3-mo follow-up after the onset of stroke.
patients (patients 1, 2, 5, and 10) were lost during 3-month follow-up after the onset of stroke. Favorable outcome (score of 0 or 1 on the modified Rankin scale) 3 months after the onset of stroke was seen in 6 patients (patients 4, 6, 8, 11, 13, and 15). Group 1 with small severe perfusion deficit had a better chance of favorable outcome at 3 months than did group 2 with medium-sized severe perfusion deficit (5 of 13 vs 1 of 4). No fatal hemorrhage occurred after thrombolysis. Only 1 (6%) of 17 patients had symptomatic small hemorrhage in the basal ganglia (Figure 3). In this patient, thrombolysis was performed 5.3 hours after the onset of acute stroke, and the extent of severe perfusion deficit was small in the presumed MCA territory, but about half of the basal ganglia was involved. Patient 17 died of sepsis on the seventh day, unrelated to thrombolysis.

**COMMENT**

Although intravenous thrombolysis with rtPA has been recommended for patients with ischemic stroke within 3 hours of onset based on the National Institute of Neurological Disorders and Stroke study,

the therapeutic time window varies from patient to patient according to the perfusion deficit and collateral blood flow. A 3-hour window is too strict for some patients who have a small ischemic core and a medium-sized to large ischemic penumbra. In previous studies, the zone of severe perfusion deficit was presumed to be the ischemic core, and the zone of moderate perfusion deficit was presumed to be the ischemic penumbra. Two patients with very small severe perfusion deficit (<10% of the presumed MCA territory) and medium-sized to large moderate perfusion deficit (patients 2 and 6) who were treated 6 to 7 hours after the onset of stroke showed early improvement within 24 hours, and 1 patient had a favorable outcome at 3 months. This study showed that intravenous thrombolysis with rtPA could be safe and effective within 3- or 7-hour therapeutic windows, when decided on the basis of the extent of severe perfusion deficit on TPCT. Thus, the current 3-hour therapeutic window for thrombolysis may be extended in patients who have a small severe perfusion deficit and a medium-sized to large moderate perfusion deficit.

Initial parenchymal hypoattenuation on precontrast CT and lesions on diffusion imaging within 24 hours of thrombolysis were confined to the zone of severe perfusion deficit on TPCT. These lesions did not recover completely on the follow-up CT scan or MRI. The zone of severe perfusion deficit might be the ischemic core. The moderate perfusion deficit may well reflect the ischemic penumbra similarly to a perfusion-diffusion mismatch on MRI. The following were supporting evidences. Individually, the initial NIHSS score correlated better with the total extent of severe perfusion deficit and moderate perfusion deficit than that of severe perfusion deficit alone on TPCT. In 3 patients (patients 2, 3, and 5), the initial lesions on diffusion-weighted imaging were confined to the zone of severe perfusion deficit on TPCT. In 4 patients (patients 1, 2, 3, and 5), the initial lesions extended into that of moderate perfusion deficit on follow-up CT or MRI (Figures 1, 2, 4, and 5).

Only 1 of 5 patients with small severe perfusion deficit and moderate perfusion deficit who probably did not...
have enough reversible zone showed early improvement after thrombolysis. In 2 of 4 patients with small severe perfusion deficit and medium-sized moderate perfusion deficit, intravenous thrombolysis resulted in early improvement. All 4 patients with small severe perfusion deficit and large moderate perfusion deficit improved within 24 hours. In only 1 of 4 patients (patient 14) with medium size of both severe perfusion deficit and moderate perfusion deficit, rtPA thrombolysis within 3 hours of onset resulted in significant improvement within 24 hours. In total, 8 patients showed early improvement.

Figure 4. Patient 5 with small severe perfusion deficit and medium-sized moderate perfusion deficit. A, Precontrast computed tomography shows hyperdense middle cerebral artery (MCA) sign (arrow) in the right MCA territory and low density in the right striatocapsular region. B, Early-phase images show decreased vascular enhancement and poor perfusion in the right temporal lobe, insula, and striatocapsular region. Middle-phase (C) and late-phase (D) images show persistent hypoattenuating areas in the right striatocapsular region (severe perfusion deficit).

Favorable outcome (score of 0 or 1 on the modified Rankin scale) 3 months after the onset of stroke was seen in 6 patients (patients 4, 6, 8, 11, 13, and 15). Four patients (patients 6, 8, 11, and 13) had small severe perfusion deficit and small or medium-sized moderate perfusion deficit without evidence of ICA or proximal MCA occlusion. Patient 4 with small severe perfusion deficit and large moderate perfusion deficit showed early improvement and favorable outcome at 3 months with recanalization of occluded ICA on magnetic resonance angiography performed on the fourth day of stroke onset.
Even if patient 15 with immediate recanalization of occluded MCA stem after thrombolysis showed only a 2-point improvement within 24 hours of thrombolysis, this patient had favorable outcome 3 months after the onset of stroke.

However, there was an inconsistency between early improvement and favorable outcome in patients 14 and 15. All 8 patients with early improvement and 6 patients with favorable outcome had no or small striatocapsular severe perfusion deficit (≤33% of the striatocapsular region). Four patients (patients 5, 10, 16, and 17) with large striatocapsular severe perfusion deficit (>50% of the striatocapsular region) had neither early improvement nor favorable outcome. Patient 9 with small severe perfusion deficit involving most of the primary motor and sensory cortex improved but still had significant disability of the affected hand. Thus, the size of severe perfusion deficit in the eloquent region, such as the striatocapsular region and the primary motor and sensory cortex, could be a factor determining early improvement within 24 hours and favorable outcome 3 months after thrombolysis.

Only patient 10 with small severe perfusion deficit and moderate perfusion deficit of the presumed MCA territory had symptomatic small hemorrhage in the basal ganglia after thrombolysis 5.3 hours after the onset of stroke. This patient had severe perfusion deficit in about half of the striatocapsular region. Symptomatic hemorrhagic transformation was not developed in 3 patients (patients 5, 16, and 17) after thrombolysis within 3 hours of onset, which had about the same size of striatocapsular severe perfusion deficit as patient 10.

There seems to be good correlation between the TPCT findings and either the baseline NIHSS score or the clinical outcome after thrombolytic therapy. However, our data should be viewed as preliminary because the number of patients studied was small. Further study is needed.

In this series there were 11 patients with ICA or proximal MCA (stem or bifurcation) occlusion. The time interval between thrombolysis and recanalization was not systematically studied in this series. Immediate recanalization after thrombolysis was confirmed only in patient 15.

We retrospectively obtained interobserver agreement in the 17 treated patients on the extent of severe perfusion deficit and moderate perfusion deficit in terms of agreement rate and the \( \kappa \) statistic. The 2 observers agreed on the small or medium-sized extent of severe perfusion deficit in all patients (\( \kappa = 1.00 \)) and on the small, medium-sized, or large extent of moderate perfusion deficit in 12 (71%) of 17 patients (\( \kappa = 0.67 \)). A \( \kappa \) value of more than 0.60 was considered to indicate substantial to excellent agreement, as suggested by Landis and Koch. 25

Triphasic perfusion CT has a disadvantage of using contrast material in patients with acute ischemic stroke. Some studies reported potential neurotoxic effects of hypotonic ionic contrast material in patients with acute infarction. 26 However, nonionic low osmolar contrast material has lower neurotoxicity and little effect on the blood-brain barrier. 27-29 Thus, we believe that the 90 mL of contrast material for TPCT will not be problematic in acute stroke patients with normal renal function.

In conclusion, this pilot study suggests that TPCT is potentially useful for selecting and triaging patients for safe and effective thrombolysis within 3 or 7 hours of stroke onset according to the extent of severe perfusion deficit on TPCT. A larger extent of moderate perfusion deficit on TPCT can predict early improvement after thrombolysis. The extent of severe perfusion deficit in the eloquent re-

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Figure 5. The same patient (patient 5) as in Figure 4. Zones of small severe perfusion deficit and medium-sized moderate perfusion deficit on the initial triphasic perfusion computed tomographic scan are shown in Figure 4. A, Diffusion-weighted magnetic resonance imaging (MRI) performed immediately after thrombolysis shows the high signal areas in the zone of severe perfusion deficit. B, Follow-up MRI 4 days after symptom onset shows that the infarct extends to the right frontotemporoparietal cortex and the subcortical white matter (moderate perfusion deficit).
gions, such as the striatocapsular region and the primary motor and sensory cortex, could be a factor to predict prognosis. Thrombolytic therapy based on the findings of TPCT or diffusion or perfusion MRI warrants a randomized clinical trial. Furthermore, TPCT may be useful in clinical trials of neuroprotective agents to select patients with mediumsized to large penumbra zones.

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