CT-Based Assessment of Acute Stroke

CT, CT Angiography, and Xenon-Enhanced CT Cerebral Blood Flow

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Background and Purpose—Only a small percentage of acute-stroke patients receive thrombolytic therapy because of time constraints and the risks associated with thrombolytic therapy. We sought to determine whether xenon-enhanced CT (XeCT) cerebral blood flow (CBF) and/or CT angiography (CTA) in conjunction with CT can distinguish subgroups of acute ischemic stroke victims and thereby better predict the subgroups most likely to benefit and not to benefit from thrombolytic therapy.

Methods—An analysis of 51 patients who had a CT, CTA, and stable XeCT CBF examination within 24 hours of stroke symptom onset was conducted. These initial radiographic studies and National Institutes of Health Stroke Scale score on admission were assessed to determine whether they could predict new infarction on follow-up CT or discharge disposition by use of the Fisher exact test to determine statistical significance.

Results—Patients with no infarction on initial CT and normal XeCT CBF had significantly fewer new infarctions and were discharged home more often than those with compromised CBF. The same held true for patients with an open internal carotid artery and middle cerebral artery by CTA and normal CT compared with those with an occluded internal carotid artery and/or middle cerebral artery by CTA. Either was superior to CT and the National Institutes of Health Stroke Scale in prediction of outcome. Both enable the selection of a group of patients not identifiable by CT alone that would do well without being exposed to the risks of thrombolytic therapy. This study included too few patients to statistically assess the role of combining CTA and XeCT CBF information.

Conclusions—The combination of CT, CTA, and Xe/CT CBF does define potentially significant subgroups of patients. The utility of this classification is supported by the observation that CTA and XeCT CBF are superior to CT alone in predicting infarction on follow-up CT and clinical outcome. This information may be useful in selecting patients for acute-stroke treatment. **(*Stroke*. 2001;32:2543-2549.)**

Key Words: angiography ■ cerebrovascular accident ■ diagnostic imaging ■ tomography ■ xenon

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Intravenous tissue plasminogen activator (tPA) administered within 3 hours of symptom onset was approved in 1996 as an effective therapy for acute stroke.[1,2] However, <5% of all patients presenting with symptoms of acute stroke are eligible to receive this treatment on the basis of current criteria.[3] Most patients are excluded because they arrive at the hospital beyond the 3-hour therapeutic window. Studies involving the use of intravenous tPA beyond the 3-hour time window have all failed to show statistical benefit on the basis of clinical and CT criteria.[4–6] Attempts to expand this time window to at least 6 hours are being made in clinical studies examining intra-arterial delivery of thrombolytics.[7,8] However, the rate of hemorrhagic complications,[9] especially when there are early signs of infarction on the CT scan,[10] continues to make physicians hesitant to administer intravenous tPA. This hesitancy is not unfounded. Two studies have demonstrated that even experienced physicians may have difficulty in consistently identifying early evidence of ischemic change on CT scans.[11,12] In addition, a CT scan does not provide information concerning the pathophysiology of the stroke.

With the development of technologies that have expanded the use of the CT scanner, in particular, CT angiography (CTA) and xenon-enhanced CT (XeCT) cerebral blood flow (CBF), it is now possible to integrate information on the location(s) of occlusion as well as a quantitative measure of CBF into acute-stroke care. This can all be accomplished in a relatively short period of time and without moving the patient after the initial CT scan. The purpose of the present study was to describe subgroups of patients by using the combined information of CT, CTA, and XeCT CBF, to hypothesize how such a categorization could affect treatment decisions, and to determine whether this classification could in part be vali-

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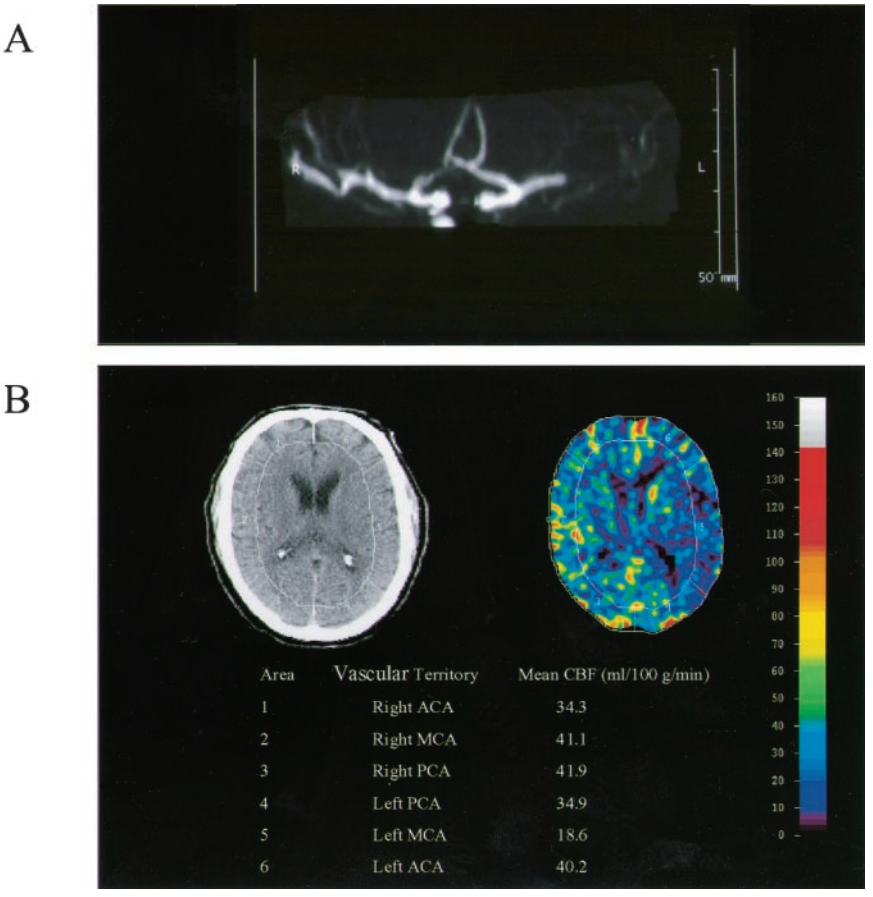

Figure 1. A, 3D reconstruction of a patient's CTA demonstrating an occluded left MCA. B, Corresponding XECT CBF study illustrating the vascular territories and demonstrating reversible CBF in the left MCA.

dated by its ability to predict follow-up infarction and discharge disposition and whether that predictive power was greater than the combination of initial National Institutes of Health Stroke Scale (NIHSS) score and CT.

Subjects and Methods

All patients undergoing CT, CTA, and XeCT CBF examinations within 24 hours of stroke symptom onset treated at our institution from September 1997 to February 2000 were identified by searching the electronic radiology records for all patients who had undergone XeCT CBF examination and then by determining what other radiological studies they had undergone. These patients were a subgroup of a larger group of patients presenting to a tertiary care stroke service with symptoms of acute hemispheric ischemic stroke. These studies were ordered by stroke teams at their own discretion, when they believed that the additional information would aid therapeutic decision making. The patients' medical records were reviewed to obtain information regarding demographics, symptoms, and treatment. Admission NIHSS scores either were taken directly from the score reported in the medical record or were calculated from the initial neurological examination contained in the medical record.[13] NIHSS scores were available for 46 patients. Scores could not be calculated for 1 patient in the 0- to 6-hour group and for 3 patients having studies after 6 hours. In the analysis of the NIHSS score as a predictor of outcome in the Trial of Org 10172 in Acute Stroke Treatment (TOAST), an NIHSS score of ≤ 6 was associated with a good outcome.[14] On the basis of this information and before statistical analysis, patients in the present study were grouped into 2 groups: those with NIHSS scores of ≤ 6 and those with scores >6.

Both the initial CT scan and a follow-up CT scan were read in a blinded and randomized manner by 1 coinvestigator (H.Y.). They were evaluated for infarction of the anterior cerebral artery (ACA), middle cerebral artery (MCA, divided into the anterior and posterior regions), and posterior cerebral artery (PCA) vascular territories.[15] They were also evaluated for infarction in the basal ganglia and deep white matter, as well as for hemorrhage, edema, and mass effect. For the purposes of the present study, the CT data were analyzed only for infarction in the MCA territory on the symptomatic side.

The CTA exams were coded on the basis of the radiology report found in the hospital's computer database (Medical ARchival System, MARS, Inc). CTA was performed on GE HiSpeed Advantage or LightSpeed scanners (GE Medical Systems). In all but 1 case, axial helical images were obtained from the level of C6 through the circle of Willis with 3-mm collimation, with reconstruction at 1-mm intervals. In 1 case, images were obtained through the intracranial circulation only, at 1-mm collimation. Images were obtained at 240 to 300 mA and 1- to 1.4-mm pitch. Scanning was begun 12 to 20 seconds after initiation of intravenous administration of 100 to 180 mL Optiray (Mallinckrodt) or 100 to 120 mL Conray (Mallinckrodt) at a rate of 2 to 3 mL per second. The CTA was defined as patent if there was no mention of occluded or stenotic vessels. The CTA was defined as occluded if either the internal carotid artery (ICA), the MCA, or both on the symptomatic side were reported to be occluded or highly stenosed (Figure 1A).

Four-level XeCT CBF studies were obtained in all patients. A computerized analysis program calculated the mean XeCT CBF within each of the 20 standardized cortical regions of interest. Patients with poor XeCT CBF confidence images were excluded. The average CBF was calculated for the ACA, MCA, and PCA territories on each study level[15] (Figure 1B). For this study, the scan level containing the lowest average flow in the MCA territory on the symptomatic side was used. On the basis of these flows, the MCA territories were assigned into 1 of 3 categories: normal ($\geq$30 mL/100 g per minute),[16] potentially reversible ischemia (7 to 29 mL/100 g per minute),[17] or irreversible ischemia ($<$7 mL/100 g per minute).[18] Because of the limited patient population, the patients with reversible CBF and the patients with irreversible CBF groups were combined

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TABLE 1. Patients Who Received Thrombolytic Therapy

Patient	Time of Initial Study, h From Onset	Initial NIHSS Score	Initial CT	XeCT CBF	CTA	Follow-Up CT	Discharge Disposition
1	<6	5	No infarct	Normal	No occlusion	No infarct	Rehab
2	<6	5	No infarct	Normal	No occlusion	No infarct	Home
3	<6	6	No infarct	Irreversible	Occluded	No infarct	Rehab
4	<6	4	No infarct	Normal	No occlusion	No infarct	Home
5	<6	8	No infarct	Normal	No occlusion	No infarct	Home
6	<6	19	No infarct	Irreversible	Occluded	Infarct	Rehab
7	<6	N/A	No infarct	Irreversible	Occluded	Infarct	Death
8	<6	8	No infarct	Reversible	Occluded	Infarct	Home
9	>6	17	No infarct	Reversible	No occlusion	No infarct	Home
10	>6	17	No infarct	Reversible	Occluded	No infarct	Rehab
11	>6	13	No infarct	Normal	Occluded	No infarct	Rehab

N/A indicates not available.

for statistical analysis. Thus, patients with normal CBF were compared with those with compromised CBF.

The primary outcome measure was defined as new infarction in the cortical MCA territory on the symptomatic side. This was determined by comparing the initial reading of the CT scan with the follow-up reading. Functional outcome was estimated by reviewing the patient's discharge disposition and categorized as home, rehabilitation facility (rehab), or death. Because of the limited patient population, the rehab and death groups were combined for statistical analyses.

A series of univariate analyses using the Fisher exact test were performed on the data to determine whether the imaging studies and NIHSS score were predictive of clinical outcome and/or cerebral infarction. In an attempt to control for the effect of treatment on outcome, the data were reanalyzed excluding the patients who received thrombolytic therapy.

Results

Patients ranged in age from 19 to 89 years (mean 61.7 years). Thirty-two (63%) patients were male, and 19 (37%) patients were female. Stroke symptoms were referable to the left hemisphere in 28 (55%) patients and to the right hemisphere in 23 (45%) patients. Patients with posterior circulation symptoms were excluded from the present study. The admission NIHSS scores ranged from 1 to 26 (mean 10.6). Concurrent treatment records detailed 8 (16%) patients receiving intravenous tPA, 2 (4%) receiving intra-arterial urokinase, and 1 (2%) receiving a combination of intravenous and intra-arterial thrombolytic therapy. The data for the 11 patients receiving thrombolytic therapy are contained in Table 1. Thirty-nine other patients (76%) were managed with antiplatelet or anticoagulant or were enrolled into investigational neuroprotective versus placebo clinical trials or some combination of the 3. Only 1 patient received no treatment.

Studies were performed within 3 hours on 14 (27%) patients, between 3 and 6 hours on 17 (33%) patients, and between 6 and 24 hours on 20 (40%) patients. The average time to completion of all 3 studies was 44.5 minutes (minimum 15 minutes, maximum 223 minutes). On the initial CT scan, 15 (29%) patients had a new infarction as determined by the presence of low attenuation in at least 50% of the MCA territory on 1 level of the CT scan on the symptomatic side. On follow-up imaging, an additional 11 patients were found to have an infarction of at least 50% of the MCA territory, bringing the total to 26 (51%). Twenty (39%) patients had normal CBF, and 31 (61%) had CBF in the ischemic range. CTA showed evidence of ICA and/or MCA occlusion in 25 (49%) patients. According to the discharge summaries, 18 (35%) patients were discharged home, 29 (57%) were discharged to rehab, and 4 (8%) patients died before discharge. The results of the initial and follow-up exams as well as the discharge disposition for all patients are detailed in Table 2.

In the group of patients presenting within 6 hours, we wanted to determine whether the presence of new infarction and discharge disposition could be predicted on the basis of the CT, NIHSS score, CTA, and XeCT CBF. In the 31 patients that were studied within 6 hours, 24 had no infarction on the initial CT scan, and 7 had an infarction. By use of the Fisher exact test, infarction on initial CT was significantly predictive of infarction on follow-up CT ($P=0.001$), as would be expected. Of particular interest are the 7 patients who had normal initial CT scans that converted to infarction, and whether or not the NIHSS score, XeCT CBF study, or CTA, in addition to the CT scan, could be used to predict which of those 24 patients would go on to infarct and which would have normal follow-up CT exams. The NIHSS score did not statistically predict new infarction on follow-up CT. Two (14%) of the 14 patients with an NIHSS score ≤ 6 and 4 (44%) of the 9 patients with an NIHSS score >6 had an infarction in the MCA territory on the follow-up CT ($P=0.162$). Of the 24 patients with no evidence of cerebral infarction on the baseline CT, 1 (8%) of the 13 patients having a normal CBF had evidence of infarction on the follow-up CT, and 6 (55%) of the 11 patients having compromised CBF had evidence of infarction on follow-up CT ($P=0.023$). A similar analysis was performed to determine whether CTA in conjunction with CT could significantly predict infarction. Only 1 (7%) of the 14 patients with an open CTA (no vascular occlusion) and no infarction on initial CT had an infarction on follow-up compared with 6 (60%) of the 10 patients with an occluded CTA (occlusion of ICA and/or MCA) and normal CT ($P=0.008$) (Figure 2).

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TABLE 2. Results of All Admission and Follow-Up Studies and Discharge Disposition for All Patients

	Initial CT		Follow-Up CT		Discharge Disposition	
Initial Exams	No Infarction	Infarction	No Infarction	Infarction	Home	Rehab/Death
Initial studies Within 6 h (n=31)						
Normal CBF, CTA open	13	0	12	1	10	13
Normal CBF, CTA occluded	0	1	0	1	0	1
Reversible CBF, CTA open	1	2	1	2	1	2
Reversible CBF, CTA occluded	7	4	3	8	2	9
Irreversible CBF, CTA occluded	3	0	1	2	0	3
NIHSS score ≤6	14	1	12	3	9	6
NIHSS score >6	9	3	5	10	4	11
Initial studies after 6 h (n=20)						
Normal CBF, CTA open	3	1	2	2	3	1
Normal CBF, CTA occluded	2	0	2	0	0	2
Reversible CBF, CTA open	3	3	1	5	2	4
Reversible CBF, CTA occluded	4	2	3	3	0	6
Irreversible CBF, CTA occluded	0	2	0	2	0	2
NIHSS score ≤6	1	2	1	2	1	2
NIHSS score >6	8	5	7	6	3	10

If the same data are analyzed regarding discharge disposition, looking only at the baseline CT, 50% of 24 patients with no infarction were discharged to home. Sixty-two percent of the 14 patients with admission NIHSS scores ≤6 were discharged to home compared with 33% of the 9 patients with admission NIHSS scores >6 ($P=0.21$). Seventy-seven percent of the 13 patients with normal CT and normal CBF by XeCT CBF were discharged to home, whereas only 18% of the 11 patients with normal CT and compromised CBF were discharged to home ($P=0.012$). Similarly, 79% of the 14 patients with a normal CT and an open CTA were discharged to home, whereas only 10% of the 10 patients with normal CT and an occluded CTA were discharged to home ($P=0.003$) (Figure 3). A statistical analysis of outcome based on all 3 tests did not reach statistical significance because the subgroup sizes were too small.

Eight patients who completed the initial imaging studies within 6 hours received thrombolytic therapy. When they were excluded from the analysis, XeCT CBF and CTA were no longer predictive of infarction on outcome CT ($P=0.26$ and $P=0.12$). Conversely, XeCT CBF and CTA remained significantly predictive of discharge disposition in patients that did not have infarctions on their initial CT scans ($P=0.04$ and $P=0.007$). The NIHSS score continued to not be significantly predictive of either the follow-up CT ($P=0.60$) or discharge disposition ($P=0.12$).

The next step was to determine whether the predictive ability of XeCT CBF and CTA in conjunction with CT extended past the 6-hour window. However, statistical significance was not reached in this group because of the limited number of patients. Of the 4 patients that had a new infarct on the follow-up CT scan, 3 had compromised CBF, but only 1 had an occluded CTA. Only 1 of the 7 patients with compromised CBF was discharged to home. No patient with an occluded CTA was discharged to home compared with 3 of the 6 with an open CTA. Using an NIHSS score of ≤6 to

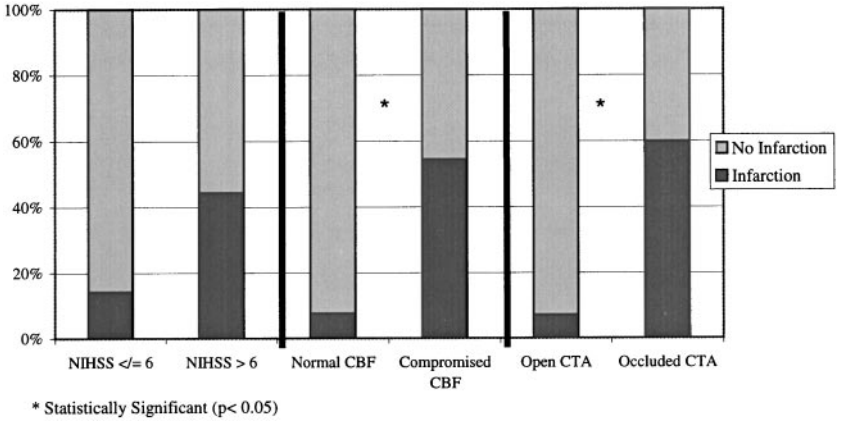

Figure 2. Infarction incidence predicted by initial NIHSS score, CBF level, and vascular patency.

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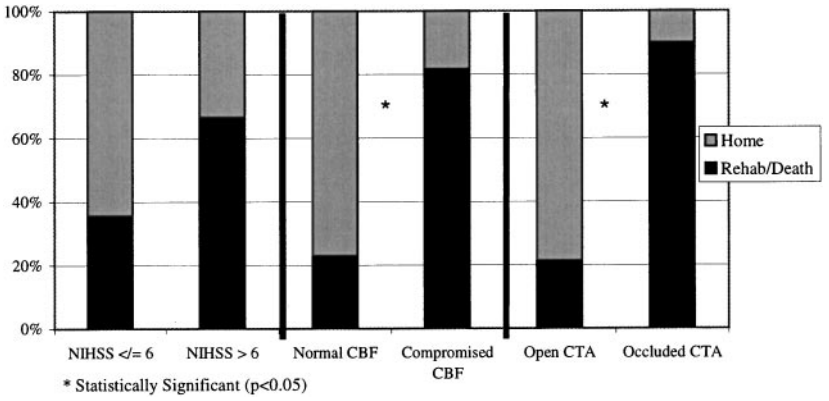

Figure 3. Discharge disposition predicted by initial NIHSS score, CBF level, and vascular patency.

predict a good outcome was not possible in the 6- to 24-hour group because only 1 of the 12 patients that did not have an infarction on the initial CT had an NIHSS score of <6.

Discussion

Currently, most patients with acute-stroke symptoms are evaluated with a noncontrast brain CT scan and clinical examination.[1,2] Standard use of neuroimaging for thrombolytic therapy with intravenous tPA patient selection consists of a noncontrast brain CT to rule out intracranial hemorrhage. The presence of infarction as manifested by low attenuation in ≥1/3 of the MCA territory is the other major radiological exclusion criterion for proceeding with thrombolytic therapy. However, the ability of a simple noncontrast brain CT to predict eventual infarction and clinical outcome in acute-stroke patients is limited. In this comparatively small study, CT combined with clinical information (NIHSS) did not predict infarction or clinical outcome, although larger studies have demonstrated that NIHSS can predict outcome.[14,19]

The XeCT CBF study allows for the rapid and quantitative assessment of CBF.[20] If compromised flow persists, quantitative values are able to discern potentially reversible (7 to 29 mL/100 g per minute) from irreversible (<7 mL/100 g per minute) ischemia.[18] XeCT CBF measurements correspond to specific cortical and subcortical areas,[21] allowing for a more accurate estimation of the volume of tissue affected by normal, reversible, or irreversible blood flow.[22,23]

Data from the present study suggest that regardless of treatment or time from symptom onset to imaging,[24] if the CBF is found to be normal (>30 mL/100 g per minute),[16] these patients are more likely to have no infarction on follow-up CT and a good functional outcome. In another study, patients who had deficits that resolved without therapeutic intervention had a mean CBF of 34.5±8.1 mL/100 g per minute.[25] Thrombolytic therapy is not likely to benefit this group of patients who presumably have already restored earlier perfusion deficits and have delayed recovery of their clinical deficits.[26] Such therapy in this subgroup may in fact be harmful, insofar as it exposes such patients to the risk of systemic bleeding complications and hemorrhagic transformation.[27] In the present study, 30% to 45% of patients had normal CBF at the time they presented for treatment. A similarly sized group was identified in the intra-arterial therapy trial.[8] The ability to consistently identify this group without the risk and expense of angiography could have a significant impact.

Patients with reversible (7 to 29 mL/100 g per minute) CBF and no initial infarction are theoretically most likely to benefit from the effects of successful thrombolytic therapy. If CBF is returned to normal levels before the onset of irreversible injury, the functional deficits might resolve, and the follow-up CT might not show new evidence of infarction.[17] Although the present study is too small to determine the predictive power of irreversible levels (<7 mL/100 g per minute) of CBF, an extensive literature with quantitative methodologies provides a solid basis for believing that patients with flow levels in this range are not likely to benefit from treatment.[18,28,29]

CTA has been demonstrated to be a quick and reliable way of determining the location of occlusion and extent of collateral flow.[30] Wildermuth et al[31] have proposed that patients should be selected for thrombolytic therapy on the basis of the identification of occlusion and the extent of leptomeningeal collateral circulation. The addition of CTA to the CT and XeCT CBF triage provides information about which blood vessel or vessels are occluded and are the probable cause for the continuing compromise of CBF. This information could theoretically aid in the selection of the most appropriate mode of delivery of thrombolytic therapy, such as whether to deliver the drug intravenously in the case of a presumed distal small-vessel occlusion, or intra-arterially in the case of an occlusion of the ICA and/or MCA.[7,8,30,31] Published data suggest that the recanalization rate for large-vessel occlusion after intravenous tPA is low.[32,33] Although this information can be obtained from conventional angiography, CTA does not carry the risks of arterial puncture and stroke secondary to catheter emboli or manipulations. CTA can also be performed within a few minutes of obtaining the baseline CT.

Intra-arterial delivery of thrombolytics has been shown to be effective in recanalizing occlusions of the MCA,[7,8] but only a select group of patients falls into this category. XeCT CBF in addition to CT and CTA not only can determine whether the collateral supply is present but also can distinguish which patients have normal, reversible (7 to 29 mL/100 g per minute), or irreversible (<7 mL/100 g per minute) flow levels. Most important is the ability to distinguish a group of

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patients with open MCA but reversible (7 to 29 mL/100 g per minute) low flow, which is presumably due to distal branch occlusion that should be most amenable to intravenous thrombolytic therapy. This group, although too few in our small study to analyze separately, cannot be identified by CTA alone.

Currently, the limiting factor in patients receiving thrombolytic therapy is the brief time from symptom onset in which therapy must be initiated, which inherently requires knowing the time of stroke onset. A substantial number of patients are found with stroke after an unknown period of time and are therefore excluded from all trials and treatments for acute stroke. Our data suggest that up to 6 hours and even between 6 and 24 hours after symptom onset, there are patients (15%) with no infarction on the initial CT and reversible ischemia by CBF criteria and/or an occluded CTA that exhibit infarction on follow-up. This group might benefit from treatments that are now only being offered to patients with a well-documented time of symptom onset and who present within the 3-hour treatment window.

In the present small study, XeCT CBF and/or CTA information in conjunction with CT was more capable of predicting new infarction and discharge disposition than was the admission NIHSS score plus CT. Only 1 patient who presented after 6 hours had an NIHSS score of <6. However, there were still patients with no infarction on follow-up CT in this subgroup that were discharged to home. In addition, the NIHSS score does not provide a guide to which method of delivery of thrombolytic therapy would have the greatest chance of being effective or which patients have already returned to normal CBF or are at higher risk of hemorrhage because of a large volume of the brain with irreversible (<7 mL/100 g per minute) CBF.[34]

One of the major caveats of predicting new infarction on CT and discharge disposition in the present study is that the results could have been affected by the type of acute-stroke therapy that some of the patients received. In an attempt to correct for this, the data were reanalyzed after excluding the patients that received thrombolytic therapy. Exclusion of these patients did not have an effect on the ability to predict clinical outcome but did lower the predictive power of XeCT CBF and CTA of infarction on follow-up CT. The weight of current evidence would support the contention that patients with normal flow, despite deficits, are likely to recover without interventions.[25]

The small number of patients studied and the large number of variables that can affect the outcome of acute-stroke patients limit the conclusions than can be drawn from the present study. At this institution, not all acute-stroke patients have been examined with CT, CTA, and XeCT CBF, and there may be a bias in the way patients were selected to have all 3 exams. Therefore, they may not be representative of the population at large. Acute-stroke therapies and poststroke complications were not accounted for in the present study. However, they may have had an effect on the discharge disposition. In addition, because of the limited number of patients, the effect of all variables did not reach statistical significance. Furthermore, the treating physicians may also have implemented treatment based on the CTA and XeCT CBF data.

A future prospective study with more patients is needed to determine whether all 3 imaging modalities together can determine which acute-stroke patients will be most likely to benefit from aggressive treatment and whether it is possible to use this physiological information to prolong the time window for acute-stroke interventions. The data presented in the present study suggest that the combination of information from XeCT CBF and CT and/or from CTA and CT can identify a subgroup of patients that, irrespective of thrombolytic therapy, will have no infarction and will be discharged to home, and that these studies can identify this important group better than the combination of NIHSS score and CT that is currently being used.

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