Background: Stroke management would benefit from a broadly available imaging tool that detects perfusion deficits in patients with acute stroke.

Objective: To determine the role of dynamic, single-slice computed tomographic (CT) perfusion imaging (CTP) in the assessment of acute middle cerebral artery stroke.

Design and Patients: Imaging with CTP and CT within the first 6 hours of symptom onset and before the start of treatment in a consecutive clinical series of 22 patients (mean age, 68.3 years; 14 women; studied within 143 ± 96 minutes of stroke onset).

Setting: A stroke unit in a university hospital.

Main Outcome Measures: Area of the perfusion deficit (nAP₀) from time-to-peak maps, hemispheric lesion area from follow-up CT (HLA₀), final infarct volume, and stroke recovery (National Institutes of Health Stroke Scale scores).

Results: Eighteen patients had perfusion deficits in the middle cerebral artery territory and corresponding hypotenuation in follow-up CT. Three patients with normal CTP findings showed lacunar infarctions or normal findings on follow-up CT. In 1 patient, CTP did not reveal a territorial deficit above the imaging slice. The overall sensitivity and specificity of CTP for the detection of perfusion deficits in patients with proven territorial infarction (n=18) on follow-up CT were 95% and 100%, respectively. The nAP₀ was significantly correlated with the National Institutes of Health Stroke Scale score at admission (P<.003) and the HLA₀ (P<.001). Different stroke patterns were identified in patients with follow-up CTP (n=10): (1) initial perfusion deficit and partial nutritional reperfusion (nAP₀>$nAP₀; n=6), (2) initial perfusion deficit and nonnutritional reperfusion (nAP₀=$nAP₀; n=2), and (3) initial perfusion deficit without reperfusion (nAP₀<$nAP₀; n=2).

Conclusions: Computed tomographic perfusion imaging detects major perfusion deficits in the middle cerebral artery territory. Because CTP is broadly available, it may play a role in acute stroke management.

Arch Neurol. 2000;57:1161-1166

Although the efficacy of intravenous thrombolytic therapy with recombinant tissue-type plasminogen activator for acute stroke was recently shown, the beneficial effect of this potentially hazardous treatment is still under discussion. One critical point that remains is the poorly defined stroke mechanism of patients enrolled in acute thrombolytic trials. The detection of malperfused brain tissue in the acute stage would help to limit thrombolysis to patients who are likely to benefit and might set the rationale for extending the therapeutic window to later time points. Different imaging strategies are available for the definition of perfusion deficits within the acute time window: (1) positron emission tomography (PET), (2) single photon emission computed tomography (SPECT), (3) xenon-CT, and (4) perfusion- or diffusion-weighted magnetic resonance imaging (MRI). All provide information on ischemic tissue; however, the application of these techniques is limited to specialized stroke centers. Especially modern MRI protocols that include diffusion- and perfusion-weighted sequences are promising tools that might provide the information necessary for acute stroke management. The combination of diffusion- and perfusion-weighted MRI might help define tissue at risk of infarction. However, at present, MRI has to prove that hemorrhages can be safely excluded and has to answer the question, “What is the therapeutic and prognostic value of deficit mismatches of diffusion- and perfusion-weighted images?”
PATIENTS AND METHODS

Patients with symptoms of acute middle cerebral artery ischemia were prospectively studied after informed consent was obtained. Patients were included if they presented with acute onset of stroke symptoms within 6 hours before CTP. Patients were excluded if they had preexisting neurologic disease or previous stroke that would hamper interpretation of imaging data, a history of hyperthyroidism, or known allergy against iodinated contrast agent. Patients with spontaneous improvement of symptoms before CTP and with abnormal CT findings not consistent with acute cerebral ischemia were excluded from further evaluation. Only patients with technically adequate CT and CTP studies were further evaluated.

The therapeutic decision was based on CT and CTP results. Patients who met National Institute of Neurological Disorders and Stroke inclusion criteria and displayed a perfusion deficit in CTP were treated with recombinant tissue-type plasminogen activator after informed consent (n=6). Patients with stroke onset within 3 to 6 hours and with extracranial (<70%) or intracranial arterial stenosis or atrial fibrillation received intravenous heparin calcium aiming to double the partial thromboplastin time. Patients with symptomatic onset within 3 to 6 hours without the above-mentioned vascular or cardiac diseases received subcutaneous low-molecular-weight heparin, aspirin (100-300 mg), ticlopidine hydrochloride (500 mg), or clopidogrel (75 mg). Patients who were eligible for participation in clinical acute stroke trials were enrolled in Therapy of Patients With Acute Stroke (n=2), the European Stroke Treatment With Ancrod Trial (n=1), or the GLYB3001-GAIN (n=1). Some patients were included in a previous study that validated the CTP methods.

CLINICAL EVALUATION

All patients were evaluated according to the National Institutes of Health Stroke Scale (NIHSS) immediately before CT and CTP (NIHSS0) and after 3 weeks (NIHSS3wk). Neurologic recovery was assessed as the difference between the NIHSS0 and NIHSS3wk scores (NIHSS0−NIHSS3wk). All clinical assessments were performed by a neurologist (J.R.) or a neurologic resident.

CT IMAGING

Eighteen axial images (120 kV, 500 mA) were acquired in the orbitomeatal orientation using a slip-ring CT scanner (Somatom Plus S; Siemens Medical System, Erlangen, Germany). Five-millimeter-thick slices with 8-mm table feed were used. Initial CT images were evaluated for early ischemic CT signs as defined by von Kummer et al. For dynamic CT perfusion studies, a series of 25 (the first 10 studies) or 40 CT scans were acquired in a single slice (120 kV, 165 mA, 10-mm slice thickness, 512 × 512 image matrix) during injection of 60 mL of nonionic contrast agent (Ultravist 300; Schering, Berlin, Germany) using a power injector (10 mL/s). The contrast agent was injected into the antecubital vein via an 18-gauge intravenous catheter. The injection was started simultaneously to the acquisition of the serial CT data. The total acquisition time was 40 seconds. A standardized slice position covering the basal ganglia; the thalamus; and parts of the anterior, middle, and posterior arterial territories was assessed (Figure).

PARAMETER MAPS AND SEMIQUANTITATIVE ANALYSIS

All CT and CTP scans were independently evaluated by a trained stroke neurologist and a radiologist (J.R. and L.J.M.) who were informed only that the CT scans were those of patients with clinically suggested stroke.

The CTP data were transferred to a SUN workstation (SUN Microsystems, Mountain View, Calif) for semiquantitative image analysis using custom software (MRVision Co, Menlo Park, Calif). Assuming that no contrast agent leaks into the parenchyma, tracer kinetics can be applied and the attenuation time curve can be transformed to a concentration time curve, since the attenuation change is linearly dependent on the amount of contrast agent in the tissue. Parameter maps of TTP, the time from the start of the contrast agent injection to the maximum bolus peak, were calculated. A TTP delay of 6 seconds or more was considered indicative of a perfusion deficit. Maps of TTP were evaluated because they proved to be a robust parameter in previous experimental and human perfusion-weighted MRI studies.

The area with a perfusion deficit was manually defined on color-coded TTP maps. Areas with perfusion deficits were then normalized to the ipsilateral hemisphere (normalized area of perfusion deficit/area of ipsilateral hemisphere × 100)). The area of hypodensity in the follow-up CT was calculated as a percentage of the hemispheric lesion area (HLA=area of hypodensity/hemispheric area × 100). The percentage of saved or lost tissue was calculated as (nAP0−HLA)/nAP0 × 100. In 10 patients with a follow-up CT study 24 hours after stroke onset (nAP1), the reperfusion area was determined in percentage as (nAP0−nAP1)/nAP0 × 100.

To address the question of how reliable a single-slice approach in the chosen location would mirror the infarct volume, the total infarct volume was calculated from the follow-up CT. The total infarct volume, expressed as a percentage of infarcted tissue normalized to the ipsilateral hemispheric volume, was then correlated with the nAP0 and the HLA.

STATISTICAL ANALYSIS

Demographic data are presented as mean±SD. The Spearman correlation coefficient was used as an estimate of the strength of association between CT, CTP variables, and clinical measures. Results were considered statistically significant at the 5% level.

Dynamic CT perfusion imaging (CTP) might overtake the role of an imaging modality that detects cerebral perfusion deficits in the acute stage and that is easily accessible to a broad community. Imaging with CTP is an easily performed add-on examination that requires a slip-ring CT scanner and takes only a few minutes. The tissue attenuation during the first pass of an intravenously applied contrast bolus through the brain tissue is tracked by serial CT acquisitions.
Patterns of computed tomographic (CT) and CT perfusion (CTP) imaging in 3 groups of patients with territorial perfusion deficits. In each panel, the upper left quadrant shows the initial CT scan and the lower left quadrant shows the initial CTP scan within 6 hours; the upper right quadrant shows the follow-up CT scan after 24 hours and the lower right quadrant shows the follow-up CTP scan. A, Six patients treated with recombinant tissue-type plasminogen activator showed reperfusion on the follow-up CTP scan and infarctions smaller than the initial area of the perfusion deficit (ie, nutritional reperfusion). B, In 2 patients treated with intravenous heparin, the area of infarction on the follow-up CT scan corresponded to the area of the initial perfusion deficit despite reperfusion on the follow-up CTP scan (ie, nonnutritional reperfusion). C, In 2 patients with recombinant tissue-type plasminogen activator therapy, reperfusion was not achieved and the area of the initial perfusion deficit corresponded to the infarction on the follow-up CT scan.

Semiquantitative parameter images of the time to peak (TTP), cerebral blood flow, mean transit time, and cerebral blood volume delineate the perfusion deficit. The obvious disadvantage of the technique is the restriction to a single-slice measurement.

We applied CTP to patients with acute stroke within the first 6 hours of stroke onset to test its utility and sensitivity for the detection of perfusion deficits. We hypothesized that (1) the single-slice approach is sensitive for the detection of major, clinically relevant perfusion deficits; (2) the area of the initial perfusion deficit in CTP correlates with the severity of stroke symptoms, clinical recovery, and final infarct size; and (3) the reperfusion area and areas of saved tissue (nutritional reperfusion) as detected by follow-up CT and CTP are useful indicators of therapeutic efficacy.

RESULTS

Three studies were excluded because of motion artifacts in CTP. Four patients with stroke onset within the 6-hour time window and known hyperthyreosis were not eligible. One patient with previously unknown hyperthyreosis developed atrial fibrillation. The remaining 22 consecutive patients were further evaluated. Ages ranged from 52 to 84 years (mean age, 68.3 years; 14 women), and the NIHSS was 13.2±5.2. The mean interval between the onset of symptoms and CT or CTP scanning was 143±96 minutes (range, 30–360 minutes).

Eighteen patients had a perfusion deficit on CTP (group A), whereas 4 patients had normal CTP results (group B). The overall sensitivity and specificity of CTP for the detection of perfusion deficits in patients with proven territorial infarction on the follow-up CT were 95% and 100%, respectively. Five patients (23%; all from group A) had early ischemic CT signs in the territory of the middle cerebral artery on the initial CT study. Hemorrhagic transformation in follow-up CT was observed in 3 patients (14%; 2 from group A and 1 from group B). The nAP0 but not final infarct volume and HLAF correlated significantly with the NIHSS3 (P<.003, Spearman correlation coefficient). Neurologic recovery, measured as the difference between NIHSS0 and NIHSS3, correlated with the reperfusion area (P<.04, Spearman correlation coefficient) but not with the percentage of lost or saved tissue.

PATIENTS WITH PERFUSION DEFICIT ON CTP (GROUP A)

Eighteen patients showed perfusion deficits on the TTP parameter maps of the initial CTP study. The mechanism of infarction according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment28 was cardioembolism in 5 patients (28%), large-artery atherosclerosis in 8 (44%), and undetermined in 6 (33%). Six patients met the National Institute of Neurological Disorders and Stroke criteria for thrombolytic treatment and received recombinant tissue-type plasminogen activator immediately after CT within the 3-hour time window. Eight patients were included 3 to 6 hours after stroke onset and received intravenous heparin, aiming to double the partial thromboplastin time. Four patients were enrolled in acute stroke trials (Therapy of Patients With Acute Stroke, the European Stroke Treatment With Ancrod Trial, and GLYB3001-GAIN) 3 to 6 hours after stroke onset. Group data are summarized in the Table.

The nAP0 correlated with the HLAF (P<.001, Spearman correlation coefficient). The infarct evolution as calculated from the difference between the nAP0 and the HLAF was expressed as the lost/saved tissue index. The mean saved tissue index was 24.3%±46.9%. The saved tissue index did not correlate with neurologic recovery. In 10 patients with follow-up CTP the first day after stroke onset the mean reperfusion area was calculated as a percentage of the nAP0 (36.3%±41.4%); the reperfusion area
correlated with neurologic recovery (P < .04, Spearman correlation coefficient).

Three different patterns of stroke evolution were observed: (1) Areas of hypoattenuation on the follow-up CT scan that were smaller than the initial perfusion deficit and showed reperfusion on the follow-up CTP scan were classified as (partial) nutritional reperfusion (nAP0 < HLAF = saved tissue; n = 6). (2) Areas of hypoattenuation on the follow-up CT scan equal to the area of the initial perfusion deficit and reperfusion in the follow-up CTP scan were classified as nonnutritional reperfusion (nAP0 = HLAF = lost tissue; n = 2). (3) Areas of hypoattenuation on the follow-up CT scan equal to the area of the initial perfusion deficits without reperfusion on the follow-up CTP scan (nAP0 < HLAF [lost tissue]; n = 2).

We addressed the question of how reliably a single-slice approach in the chosen location would mirror the total infarct volume and found that the nAP0 and the HLAF significantly correlated with the final infarct volume (nAP0: P < .008; HLAF: P < .001, Spearman correlation coefficient).
the neurologic symptoms at stroke onset (NIHSS0). The
farct volume of follow-up CT studies and the severity of
studies, correlated with neurologic recovery. These find-
reperfusion area, as calculated from 2 consecutive CTP
pean Cooperative Acute Stroke Study I criteria29) might
middle cerebral artery territory (according to the Euro-
deficit and CT hypodensity less than one third of the
derived information on a mismatch between perfusion
can be limited to patients with stroke with CTP-proven
 Stroke might benefit from CTP 2-fold: (1) thrombolysis
duced these findings.8,30
Follow-up studies using CTP discriminated different
patterns of stroke evolution: (1) Patients with nutritional
perfusion deficit that depicted infarctions smaller than the
nAP0, thus indicating the salvage of tissue at risk. In
these patients, saved tissue correlated with neurologic re-
covery. (2) Patients with nonnutritional reperfusion and
final infarct size corresponding with the nAP0. (3) Pa-
ents without reperfusion and final infarct size corre-
spending with the nAP0. Similar patterns of stroke evo-
lution previously have been described in a single photon
emission CT study30 and are valuable indicators of stroke
evolution.
The drawback of CTP is the restriction to a single-
slice approach. However, if applied on the suggested level
through the basal ganglia, the sensitivity for the detec-
tion of territorial perfusion deficits is high (95%). The
population being studied is biased toward patients with
perfusion deficits and severe neurologic deficits be-
cause patients with acute stroke with severe neurologic
deficits are admitted to the hospital faster. Despite this
limitation, with the exception of one false-negative study,
small-vessel disease was the presumable stroke mecha-
nism in cases of normal CTP findings.
One might argue that CT angiography performed
instead of CTP provides useful information about intrac-
ranial artery disease.31-33 We find that CTP delivers func-
tional information about tissue perfusion that is not avail-
able from CT angiography and that artery disease and
vessel patency can be likewise assessed by transcranial
Doppler sonography and transcranial color-coded du-
plex sonography.34,35 The major drawback of CTP, namely,
the limitation to a single slice, will be overcome by the
new generation of multi-ring CT systems.
In conclusion, future acute stroke trials might use
an imaging protocol applicable to a multicenter setting
that identifies patients who are eligible for thrombolysis
and yields basic parameters of treatment efficacy. Be-
cause CTP is ubiquitously available, it might well over-
take this role. The diagnostic value of CTP may be en-
chanced by combination with transcranial Doppler
sonography and transcranial color-coded duplex sonog-
raphy. The clinical value of CTP in patient selection for
thrombolysis during the first hours of acute ischemic
stroke remains to be determined within a larger prospec-
tive clinical trial.

Accepted for publication January 25, 2000.
Reprints: Joachim Roether, MD, University Hospital
Hamburg Eppendorf, Department of Neurology, Mar-
tinistr. 52, 20246 Hamburg, Germany (e-mail: roether@uke.
.uni-hamburg.de).

REFERENCES

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study

<table>
<thead>
<tr>
<th>Reperfusion Area, %</th>
<th>Therapy</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>100.0</td>
<td>Heparin</td>
<td>LA</td>
</tr>
<tr>
<td>NA</td>
<td>Heparin</td>
<td>LA</td>
</tr>
<tr>
<td>39.6</td>
<td>Aspirin/LMWH</td>
<td>LA</td>
</tr>
<tr>
<td>NA</td>
<td>Aspirin</td>
<td>LA</td>
</tr>
<tr>
<td>38.1</td>
<td>Ancrod, clopidogrel</td>
<td>LA</td>
</tr>
<tr>
<td>49.7</td>
<td>Ticlopidine</td>
<td>LA</td>
</tr>
<tr>
<td>36.3 ± 41.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NA</td>
<td>Heparin</td>
<td>SVO</td>
</tr>
<tr>
<td>NA</td>
<td>Heparin</td>
<td>CE</td>
</tr>
<tr>
<td>36.3 ± 41.4</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>


©2000 American Medical Association. All rights reserved.

Downloaded From: by a Non-Human Traffic (NHT) User on 11/09/2018
2. Grotta J. Should thrombolytic therapy be the first-line treatment for acute isch- 
eic stroke? t-PA—the best current option for most patients [see comments]. 
3. Wardlaw JM, Warlow CP, Counsell C. Systematic review of evidence on throm-
bolytic therapy for acute ischaemic stroke [see comments]. Lancet. 1997;350: 
607-614.
the first-line treatment for acute ischemic stroke? Thrombolysis—not a panacea 
for ischemic stroke [see comments]. N Engl J Med. 1997;337:1309-1310; dis-
cussion 1313.
reperfusion: a positron emission tomography study in systemic recombinant tis-
 sue plasminogen activator thrombolysis of acute stroke. J Cereb Blood 
7. Furlan M, Marchal G, Vader F, Derlon JM, Baron JC. Spontaneous neurological 
recovery after stroke and the fate of the ischemic penumbra [see comments]. 
on reperfusion and recanalization: Australian Streptokinase Trial Study Group. 
Technetium-ethyl-cysteinate-dimer single-photon emission CT can predict fatal 
11. Baird AE, Austin MC, McKay WJ, Donnan GA. Changes in cerebral tissue perfu-
sion during the first 48 hours of ischemic stroke: relation to clinical outcome. 
12. Grotta JC, Alexandrov AV. t-PA-associated reperfusion after acute stroke dem-
onstrated by SPECT [see comments]. Stroke. 1998;29:429-432.
13. Firlik AD, Kaufmann AM, Wechsler LR, Firlik KS, Fukui MB, Yonas H. Quantita-
tive cerebral blood flow determinations in acute ischemic stroke: relationship to 
computed tomography and angiography [published correction appears in Stroke. 
 cerebral blood volume in acute human stroke by use of single-slice dynamic sus-
etibility contrast-enhanced magnetic resonance imaging. Stroke. 1996;27: 
1088-1093.
16. Barber PA, Darby DG, Desmond PM, et al. Prediction of stroke outcome with 
echoplanar perfusion- and diffusion-weighted MRI. Neurology. 1998;51:418- 
426.
with combined multisection diffusion-weighted and hemodynamically weighted 
18. Tong DC, Yenari MA, Albers GW, O’Brien M, Marks MP, Moseley ME. Correla-
tion of perfusion- and diffusion-weighted MRI with NIHSS score in acute (<6.5 
19. Shih TT, Huang KM. Acute stroke: detection of changes in cerebral perfusion with 
brain: techniques, data analysis, and applications. AJR Am J Roentgenol. 1981; 
136:759-770.
21. Nagata K, Asano T. Functional image of dynamic computed tomography for the 
22. Tornyiama T, Tanizaki Y, Hongo K, Osawa M, Kobayashi S. Functional image of 
dynamic computed tomography in diagnostic and prognostic evaluation of is-
 chemic stroke within the first 6 hours. Stroke. 1993;24:1933-1944.
23. Koenig M, Klotz E, Luka B, Venderink DJ, Spittler JF, Heuser L. Perfusion CT of 
the brain: diagnostic approach for early detection of ischemic stroke. Radiol-
tic value of early CT in occlusion of the middle cerebral artery trunk. AJNR Am J 
26. Axel L. Cerebral blood flow determination by rapid-sequence computed tomog-
27. Rüther J, de Crespinig AJ, D’Arceul H, Iwai K, Moseley ME. Recovery of appar-
tent diffusion coefficient after ischemia-induced spreading depression relates to 
ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of 
tissue plasminogen activator for acute hemispheric stroke: the European Coop-
the CT angiography in acute ischemic stroke [see comments]. AJNR Am J Neuro-
32. Shrier DA, Tanaka H, Noguchi Y, Konno S, Patel U, Shibata D. CT angiogra-
phy in the evaluation of acute stroke [see comments]. AJNR Am J Neuroradiol. 
angiography in patient selection for thrombolytic therapy in acute hemispheric stroke. 
34. Postert T, Braun B, Federlein J, Prazuntek H, Koster O, Butten T. Diagnosis and 
monitoring of middle cerebral artery occlusion with contrast-enhanced tran-
scranial color-coded real-time sonography in patients with inadequate acoustic 
35. Goertler M, Kross R, Baeumer M, et al. Diagnostic impact and prognostic re-
levance of early contrast-enhanced transcranial color-coded duplex sonography in 