Early X-Ray Hypoattenuation of Brain Parenchyma Indicates Extended Critical Hypoperfusion in Acute Stroke

M. Grond, MD; R. von Kummer, MD; J. Sobesky, MD; S. Schmülling, MD; J. Rudolf, MD; K. Terstegge, MD; W.-D. Heiss, MD

Background and Purpose—The presence of early x-ray hypoattenuation is an important selection criterion for thrombolytic therapy. However, knowledge about the pathophysiological constellation reflected by this hypoattenuation is lacking. Our objective was to study the relationship between the presence of early CT hypoattenuation and the volumes of critical cortical hypoperfusion.

Methods—In 32 patients with acute ischemic stroke, CT was performed 20 to 170 minutes (mean, 94 minutes) after symptom onset, and \([^{15}\text{O}]\text{H}_2\text{O-PET}\) 20 to 120 minutes (mean, 67 minutes) later. CTs were scrutinized for the presence of hypoattenuation. On the PET scans, the volumes of critical cortical hypoperfusion were assessed.

Results—CT hypoattenuation was present in 18 patients (56%), all of whom had critical cortical hypoperfusion and developed infarction. Of the 14 patients with normal CTs, critical hypoperfusion was found in 6, and 7 developed infarction. The mean volumes of critically hypoperfused tissue differed significantly \((P=0.0001, \text{Wilcoxon test})\) between the CT normal (mean 13.9 cm\(^3\), range 0 to 71 cm\(^3\)) and the CT abnormal (mean 116.3 cm\(^3\), range 4 to 389 cm\(^3\)) groups.

Conclusions—Early presence of hypoattenuation is indicative of extended volumes of critically hypoperfused cortical tissue. The extent of hypoperfusion may exceed that of hypoattenuation, and some of that tissue might still be salvageable. (Stroke. 2000;31:133-139.)

Key Words: stroke, acute \(\bullet\) computed tomography \(\bullet\) positron emission tomography

The target of therapeutic intervention for ischemic stroke is ischemic tissue that is not yet irreversibly injured.1 The identification of such tissue is desirable as a prerequisite for aggressive therapeutic interventions, such as thrombolysis.

CT is available at most hospitals treating stroke patients and thus remains the only clinically practical imaging tool to guide hyperacute stroke therapy. Unenhanced CT does not reliably show either the arterial occlusion or the extent of disturbed cerebral perfusion. It was recently shown, however, that the success of thrombolysis within a 6-hour time window was associated with the initial CT findings.2 In patients with subtle hypoattenuation in a restricted area, <33% of the middle cerebral artery (MCA), the benefit from recombinant tissue plasminogen activator treatment was more pronounced than in patients with normal CT at baseline. This observation suggests the presence of ischemic tissue at risk of infarction that might be salvaged by thrombolysis, in addition to the hypoattenuated and presumably already irreversibly damaged tissue. The purpose of our study was to test the hypothesis that x-ray hypoattenuation detected by CT within 3 hours of stroke onset represents the core of severe cerebral ischemia with irreversibly damaged tissue surrounded by ischemic but potentially viable tissue. For that purpose, we assessed cerebral perfusion with PET early after CT.

Subjects and Methods

Patient Selection and Management

Between March 1996 and May 1998, 32 patients with acute ischemic stroke were admitted to our Neurological Department within 3 hours of symptom onset and during operating hours of the PET unit. Preliminary observations in 23 patients of this cohort have been published in a research letter.3 On admission, neurological deficit was assessed according to the National Institutes of Health Stroke Scale (NIHSS, 0 to 42 points).4 Twenty-six patients were eligible for systemic thrombolysis and were treated according to the NINDS protocol as described earlier in detail.5 Thrombolysis was initiated either shortly before or during PET scanning. Six patients did not receive thrombolysis: 1 had major early infarct signs on CT, 1 did not give his consent, and 4 had been studied before thrombolysis was introduced as a therapeutic option in our department.

CT Studies

Unenhanced head CT scanning with a Siemens Somatom Plus 32 scanner was routinely performed on admission with a slice thickness...
of 4 mm from the occipital foramen to the sellar region and 8 mm above. CT scans were scrutinized for early abnormalities, defined as parenchymal hypoattenuation or cortical effacement by an experienced neuroradiologist (R.v.K.) blinded to clinical symptoms, follow-up CT and MRI, and PET information. The abnormalities were delineated manually on the CT scans. Patients were then subdivided into the following groups: (1) CT normal and (2) CT abnormal: (A) hypoattenuation restricted to basal ganglia, (B) hypoattenuation of basal ganglia and cortex <33% of the MCA territory, (C) hypoattenuation restricted to the cortex <33% of the MCA territory, and (D) hypoattenuation of basal ganglia and cortex >33% of the MCA territory. Focal brain tissue swelling with cortical effacement was recorded but was not analyzed further. After 2 to 3 weeks, unenhanced CT was used to assess the final infarcted area in all 29 surviving patients. In 3 patients who died before that time point, the last follow-up CT served as reference. The final infarction was manually delineated by one of us (J.R.) blinded to any other information. Then location and extent of final infarction were visually compared with location and extent of early CT hypoattenuation by 2 independent, experienced neurologists (S.S., M.G.). They assessed to what extent (completely or partly) initially hypoattenuated tissue turned into infarction.

**PET Studies**

Cerebral blood flow was measured immediately after CT. PET studies were performed on an ECAT EXACT HR scanner (Siemens/CTI) in a 2D data acquisition mode providing 47 contiguous 3-mm slices at 5-mm full width at half maximum in-plane reconstructed resolution. CBF was measured according to the [15O]H2O IV bolus method, with 60 mCi used for each study. However, since arterial blood samples could not be obtained in the majority of patients because they were eligible for intravenous thrombolytic treatment, regional tracer uptake was determined voxel by voxel in the cortex of the affected hemisphere, and the percentage ratio to the mean of the contralateral hemisphere was used as a relative measure of perfusion. The threshold of critical cortical hypoperfusion was operationally set to 50% [15O]H2O uptake. In a previous quantitative CBF-PET study of patients with acute ischemic stroke, this perfusion level was shown to correspond to cortical blood flow of <12 mL · 100 g⁻¹ · min⁻¹, which represents the widely accepted threshold of critical hypoperfusion. Postacquisition coregistration of PET and CT data was not possible because the slice thickness of the routine CT scans was too large. Thus, resolution of the CT scans in the z direction was too low in comparison with PET scans to allow a 3D volume reconstruction and 3D matching. Because we had no exact anatomic guidance, we assessed blood flow only in the cortex, not in the subcortical structures. The cortical rim was defined on the PET scans. Because the inner boundaries could hardly be demarcated in the affected areas, the cortical rim was first manually delineated under visual control on the unaffected hemisphere and then mirrored to the side of the infarction (Figure 1). The volume of critical cortical hypoperfusion was then assessed by thresholding (uptake <50%) the cortical rim. Volumes of hypoperfusion <1 cm³ were ignored to reduce the probability of including technical artifacts.

**Statistics**

The volume of critically hypoperfused cortical tissue was compared between the CT normal and the CT abnormal groups by Wilcoxon’s signed rank test. After median dichotomy of the volume of hypoperfusion values, Fisher’s exact 2-tailed test was performed to analyze the association between the presence of CT hypoattenuation (normal versus abnormal) and the extent of cortical hypoperfusion.
To assess whether there was critical hypoperfusion beyond the hypotenuated areas, patients without cortical involvement on CT, namely those with hypoattenuation confined to the basal ganglia, were analyzed separately.

**Results**

Thirty-two patients (19 men, 13 women) 48 to 76 years old (mean 65 years) were entered into our study (Table). CT was performed 20 to 170 minutes (mean 94 minutes) after symptom onset, and PET 20 to 120 minutes (mean 67 minutes) later. Critical cortical hypoperfusion of $1 cm^3$ was present in 24 patients (75%) and x-ray hypoattenuation in 18 patients (56%); in 10 patients, hypoattenuation was restricted to the basal ganglia (A); in 3, additional hypoattenuation was found in the cortex covering $<33%$ of the MCA territory (B); in 2, covering $>33%$ of the MCA territory (D); and in 3, hypoattenuation was restricted to the cortex (C). Two of the patients with basal ganglia hypoattenuation (group 2A) exhibited additional cortical effacement. Patients with early CT hypoattenuation ($n=18$) did not differ with respect to age or interval between symptom onset and CT or PET study, respectively, from those with normal initial CT scans ($n=14$). However, they had higher initial NIHSS scores (median NIHSS 14 versus 9, $P=0.01$).

Infarcts covering the entire area of initial hypoattenuation developed in all patients with early CT hypoattenuation, but also in 7 of the 14 patients with normal initial CT. In 1 of the 2 patients with cortical effacement, this area did not turn into infarction (Figure 2), and in the other patient it did (Figure 3). In all 18 patients with CT hypoattenuation, critically hypoper-
fused cortical tissue was found on the PET, but also, in 6 of 14 patients with normal CT scan, there was critical cortical hypoperfusion of \(1c m^3\). In 7 of 24 patients with critical cortical hypoperfusion of \(>1 cm^3\) (patients 9, 10, 11, 15, 18, 19, and 20), no cortical infarction developed: all of them had received thrombolysis. Of 8 patients without \(\leq 1 cm^3\) critical cortical hypoperfusion, no one had hypoattenuation on CT, and only 1 (patient 3) developed cortical infarction. This patient had not received thrombolysis.

The mean volume of critically hypoperfused tissue differed significantly \((P=0.0001, \text{ Wilcoxon test})\) between the CT normal (mean 13.9 cm\(^3\), range 0 to 71 cm\(^3\)) and the CT abnormal (mean 116.3 cm\(^3\), range 4 to 389 cm\(^3\)) groups. After median dichotomy of the volume-of-hypoperfusion values, Fisher’s exact 2-tailed test revealed a close association between the presence of CT hypoattenuation and the extent (small versus large) of cortical hypoperfusion \((P<0.002)\).

In the separate comparison between the 10 patients with pure basal ganglia hypoattenuination and the group without CT hypoattenuation, similar results were obtained. The volume of critically hypoperfused cortical tissue differed significantly \((P=0.0004)\) between the CT normal (mean 13.9 cm\(^3\), range 0 to 71 cm\(^3\)) and the CT basal ganglia abnormal (mean 139 cm\(^3\), range 4 to 389 cm\(^3\)) groups. There was also a close association between the presence of basal ganglia CT abnormalities and the extent of cortical hypoperfusion \((P<0.002)\).

On the final CT, the ischemic lesion had extended from the basal ganglia to the cortex in 7 of these 10 patients, in 6 despite thrombolytic treatment.

**Discussion**

The ideal diagnostic tool for the management of acute ischemic stroke should be noninvasive, provide information on the severity and extent of hypoperfusion, and assess the proportion of already irreversibly damaged tissue.

Hypoattenuation on CT indicating ischemic edema\(^{12}\) was frequent (56%) and highly predictive of definitive infarction.
in our study (positive predictive value of 100%). Even with early thrombolytic treatment, the development of infarction could not be prevented in hypoattenuated areas. This is in accordance with the ECASS II findings, in which hypoattenuated tissue turned into necrosis with a probability of 97% (95%, CI 95% to 98%). The extent of hypoattenuation on CT, however, might underestimate the extent of critical ischemia, especially at an early time point, because at that stage the increase in tissue water may still be too small to become visible on CT. As demonstrated, all 10 patients with hypoattenuation restricted to basal ganglia also had critical cortical hypoperfusion, and in 7 of them, the ischemic lesion extended from the basal ganglia to the cortex. Also, in 6 of 14 patients without hypoattenuation, critical cortical hypoperfusion was found; all received thrombolysis, and cortical infarctions developed in only 2 of them. Therefore, patients with a normal CT should not a priori be excluded from aggressive therapy. Because of the delayed appearance of ischemic edema, negative CT findings are of limited predictive value at that early stage (<3 hours).

Flow studies can provide information on the severity and extent of hypoperfusion but not on tissue integrity. Flow changes are present at symptom onset, but their extent may vary in the dynamic process of cerebral ischemia. In the very early phase, the area of hypoperfusion is equivalent to the area of tissue at risk, and its assessment may be helpful for therapeutic decisions. Whether or not hypoperfusion leads to necrosis depends not only on severity but also on duration of hypoperfusion. This may explain the limited predictive value of CBF measurements alone at only 1 time point. In 17 of 24 patients with critical cortical hypoperfusion, cortical infarcts developed, in most cases despite thrombolytic therapy. All 7 patients in whom no infarcts developed had received thrombolytic therapy. This is in accordance with recently published findings that even critically hypoperfused tissue can be salvaged by early reperfusion. The positive

Figure 3. Initial CT and PET of a 75-year-old woman with severe left-sided hemiparesis (initial NIHSS, 16 points) treated with thrombolysis 105 minutes after symptom onset. a and b, CT scan 73 minutes after symptom onset. Hypoattenuation of right basal ganglia (a) and additional cortical effacement (b). c and d, Corresponding transaxial CBF [15O]H2O PET slices 62 minutes after CT, showing critical hypoperfusion (185 cm³). e and f, Corresponding follow-up CT scans 4 days later. Large MCA infarction including the region of initial hypoattenuation and cortical effacement. Flumazenil precisely predicted the extension of final infarction.
predictive value of early critical hypoperfusion cannot be
derived from our data because most patients were treated with
thrombolysis. No data on the natural course of such patients
are available at present. However, in the 8 patients in whom
no critical cortical hypoperfusion was found, there was no
hypoattenuation on CT, and cortical infarction developed in
only 1. This patient was not treated with thrombolysis. Again,
the spontaneous prognosis of such patients remains
undetermined.

The combination of CT and flow measurements in our
study demonstrated that early hypoattenuation on CT not only
indicates irreversible tissue damage but also yields indirect
information about the cerebral perfusional state of the patient.
The presence of hypoattenuation at that early stage, as in our
population within the first 3 hours after symptom onset,
reflects severe hypoperfusion in those areas. In the case of
basal ganglia hypoattenuation, such findings are indicative of
proximal MCA occlusion. In those patients, not only the
basal ganglia but also, depending on the extent of collateral
flow, large parts of the cortical MCA territory are threatened
with ischemia. These patients may be regarded as high-risk
patients in whom ischemia has already caused irreversible
damage in the basal ganglia but also jeopardizes extended
cortical areas that might be salvaged by early reperfusion. They
should receive treatment urgently, without delay.

Parenchymal hypoattenuation and cortical effacement
indicating brain swelling might represent 2 different entities
with different prognostic significance. Whereas parenchymal
hypoattenuation is highly predictive of irreversible tissue
damage, the fate of swollen brain tissue has not been
sufficiently analyzed. As shown in Figures 2 and 3, areas with
focal swelling may be salvaged from infarction (Figure 2),
but in other cases they may become irreversibly damaged
despite thrombolytic therapy (Figure 3).

The major limitation of the early CT abnormalities is their
subtlety, which makes evaluation difficult. It was recently
reported that there is considerable lack of agreement, even
among experienced clinicians, in recognizing and quantifying
early CT abnormalities. Among the investigators, however,
the findings of 1 neuroradiologist served as the gold standard.
To assess the quality of this gold standard, they evaluated
whether the CT finding location was included in the lesion
location at 24 hours. The positive predictive value was 96% (95% CI, 92% to 100%). We also used the follow-up CT as
an internal control to assess the quality of the CT reading. All
hypodense areas determined by the neuroradiologist on the
baseline CT became infarctions on the follow-up scans (100% positive predictive value). These findings imply that
the correct evaluation of early hypoattenuation is learnable.
As demonstrated, adequate training helps to improve the
detection of early infarct signs and should therefore be
required for all physicians engaged in acute stroke manage-
ment. Expert CT reading, as recommended by the AHA
Stroke Council, is important not only for identification of
early infarct signs but also for reliable detection of hemorrhage.

One limitation of our study is that there was a 1-hour
difference between CT scans and PET scans. However, such
time delay is unavoidable in comparative studies, and all
efforts were undertaken to keep this time interval as short as possible. The fact that thrombolysis was initiated shortly
before or during PET scanning should not have influenced
cerebral blood flow, because recanalization is a
 time-
consuming process that usually takes ∼2 hours even in local
thrombolysis.21

In the future, CT may be replaced by new MRI technology.22
Combined diffusion- and perfusion-weighted imaging might be able to outline irreversible tissue damage and to
suggest the existence of a penumbra.23,24 However, diffusion
changes were recently reported to be present and also
reversible in patients with transient ischemic attack.25 Therefore,
more basic and clinical work needs to be done before this
technique can be used reliably in clinical routine.26,27 In
addition, in the near future, this sophisticated and expensive
technique will not be available in most community hospitals,
which currently treat the majority of stroke patients.

In conclusion, our observations illustrate that subtle CT
abnormalities are frequently found in patients eligible for
thrombolysis within 3 hours after onset of symptoms. Tissue
hypoattenuation, detected by CT, indicates irreversible dam-
age within this region. PET demonstrates that CT might
reflect only the most severely affected part, ie, the tip of the
iceberg, and underestimate the extent of ischemically com-
promised but potentially salvageable tissue.

References
1. Fischer M. Characterizing the target of acute stroke therapy. Stroke. 1997;
  28:866–872.
2. von Kummer R, Allen KL, Holle R, Bozzo L, Bastianello S, Manefle C,
Bluhmki E, Ringleb P, Meier DH, Hacke W. Usefulness of early CT
computed-tomography abnormalities in acute stroke. Lancet. 1997;350:
  1595–1596.
EC, Grotta J, and the NINDS TPA Stroke Study Group. Improved
reliability of the NIH stroke scale using video training. Stroke. 1994;25:
  2220–2226.
5. Grond M, Stenzel C, Schmuhl S, Rudolf J, Neveling M, Lechleuthner
A, Schneweis S, Heiss W-D. Early intravenous thrombolysis for acute
ischemic stroke in a community-based approach. Stroke. 1998;29:
  1544–1549.
U, Heiss W-D. The ECAT EXACT HR: Performance of a new high
7. Herskovic P, Markham J, Raichle ME. Brain blood flow measured with
  782–789.
8. Heiss WD, Thiel A, Grond M, Graf R. Which targets are relevant for
ischemic CBF using 15 O-H 2 O-PET without arterial blood sampling. In:
Carson R, Duabe-Witherspoon M, Herskovic P, eds. Quantitative Func-
tional Brain Imaging With PET. San Diego, Calif: Academic Press;
MG, Comar D. Local interrelationships of cerebral oxygen consumption
and glucose utilization in normal subjects and in ischemic stroke patients:
a positron tomography study. J Cereb Blood Flow Metab. 1984;4:
  140–149.
and cerebral metabolic rate of oxygen requirements for cerebral function
12. Ianotti F, Holt J. Ischemic brain edema with and without reperfusion: an


Early X-Ray Hypoattenuation of Brain Parenchyma Indicates Extended Critical Hypoperfusion in Acute Stroke


*Stroke*. 2000;31:133-139
doi: 10.1161/01.STR.31.1.133

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/31/1/133

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/