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

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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 $^{15}$O]H$_2$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 ($P=0.0001$, Wilcoxon test) between the CT normal (mean $13.9 \text{ cm}^3$, range $0$ to $71 \text{ cm}^3$) and the CT abnormal (mean $116.3 \text{ cm}^3$, range $4$ to $389 \text{ cm}^3$) 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 ▪ computed tomography ▪ positron emission tomography

The target of therapeutic intervention for ischemic stroke is ischemic tissue that is not yet irreversibly injured. 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. 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. On admission, neurological deficit was assessed according to the National Institutes of Health Stroke Scale (NIHSS, 0 to 42 points). Twenty-six patients were eligible for systemic thrombolysis and were treated according to the NINDS protocol as described earlier in detail. 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 selle 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 $\left[^{15}\text{O}\right]\text{H}_2\text{O}$ 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% $\left[^{15}\text{O}\right]\text{H}_2\text{O}$ 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 $<12 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, 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 $\leq 1 \text{ cm}^3$ 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 hypoattenuated 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 cm³ 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 hypoperfu-
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 $\geq 1$ cm$^3$. In 7 of 24 patients with critical cortical hypoperfusion of $\geq 1$ 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 ($P=0.0004$, Wilcoxon test) between the CT normal (mean 13.9 cm$^3$, range 0 to 71 cm$^3$) and the CT 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 (195 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.
The 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.15 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 irreversible damage in the basal ganglia but also jeopardizes extended cortical areas that might be salvaged by early reperfusion.15 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.17 Among the investigators, however, the findings of 1 neuroradiologist served as the gold standard. To assess the quality of the 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,18 adequate training helps to improve the detection of early infarct signs and should therefore be required for all physicians engaged in acute stroke management. Expert CT reading, as recommended by the AHA Stroke Council,19 is important not only for identification of early infarct signs but also for reliable detection of hemorrhage.20

One limitation of our study is that there was a 1-hour difference between CT scans and PET scans. However, such a 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 \( \approx 2 \) 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 damage 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 compromised but potentially salvageable tissue.

References


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