Iomazenil–Single-Photon Emission Computed Tomography Reveals Selective Neuronal Loss in Magnetic Resonance-Defined Mismatch Areas

Dorothee Saur, MD; Ralph Buchert, PhD; Rene Knab, MSc; Cornelius Weiller, MD; Joachim Röther, MD

Background and Purpose—The mismatch of hypoperfused tissue on perfusion imaging and ischemic tissue on diffusion-weighted imaging is used as a surrogate marker for thrombolytic therapy in the extended time window. Mismatch tissue may recover completely, progress toward infarction, or proceed toward incomplete infarction with selective loss of cortical neurons. We used $^{[123]}$Iomazenil–single-photon emission computed tomography (IMZ-SPECT) to characterize the neuronal integrity of reperfused “tissue at risk of infarction” that appeared morphologically intact on follow-up magnetic resonance imaging (MRI).

Methods—Twelve patients with acute stroke with striatocapsular (SC) infarctions were examined with multimodal MRI at days 0, 1, and 7; IMZ-SPECT was performed at days 5 to 15. The PI at day 0, fluid-attenuated inversion recovery (FLAIR) image at day 7, and IMZ-SPECT were coregistered and stereotactically normalized. The mismatch volume of interest (VOI) was defined as the initial PI lesion subtracted by the FLAIR lesion at day 7. An asymmetry ratio (AR) was computed by dividing the mean IMZ uptake of the mismatch VOI by the unaffected mirror VOI. The same AR was computed for signal intensity on FLAIR images at day 7. Three patients with cortical infarctions were included for calibration of the AR. In this group, the VOI consisted of the FLAIR lesion at day 7.

Results—All patients with SC infarctions had a large mismatch of initially hypoperfused (112±31 mL; mean±SD) and finally infarcted tissue (19±14 mL). Mean AR of cortical IMZ uptake was 0.85±0.01 in cortical infarctions and 0.95±0.03 in SC infarctions; thereby AR showed a continuous distribution from clearly reduced (0.89) to normal (1.01) in SC infarctions. Mean AR for FLAIR signal intensity was 1.84±0.14 for cortical infarctions and normal (1.01±0.03) for SC infarctions.

Conclusions—IMZ-SPECT detected a selective loss of cortical neurons in patients with SC infarctions in transient hypoperfused tissue, which was morphologically intact on MRI. (Stroke. 2006;37:2713-2719.)

Key Words: cerebral ischemia ▪ diffusion and perfusion imaging ▪ incomplete infarction ▪ iomazenil-SPECT ▪ mismatch tissue

Incomplete infarction is defined as a selective loss of cortical neurons with survival of glial cells and vascular elements and may occur after moderate ischemia (eg, regional blood flow of 15 to 20 mL/min per 100 g).1 Garcia and colleagues demonstrated the phenomenon at histopathologic preparations of rat brains. After arterial occlusion of 10 to 25 minutes, they observed a selective neuronal necrosis and various glial responses.2 Such an incomplete infarction usually remains undiscovered on conventional magnetic resonance imaging (MRI).3 Single-photon emission computed tomography (SPECT) with $^{[123]}$Iomazenil (IMZ) as a specific ligand of the central benzodiazepine receptor provides measures of the local availability of benzodiazepine receptor, which are largely independent from local blood flow changes.4 The benzodiazepine receptor is part of the postsynaptic GABA receptor complex and present in high concentration on all intact cortical neurons. Thus, IMZ-SPECT offers the possibility to quantify the density of intact cortical neurons and to differentiate complete from incomplete infarction after focal cerebral ischemia.5 Nakagawara and colleagues first demonstrated incomplete infarction with IMZ-SPECT in patients with reperfused cortex in tissue that appeared structurally intact on MRI scans.3

Diffusion-weighted imaging (DWI) in combination with perfusion imaging (PI) has become a widely accepted modality for the selection of patients for acute reperfusion therapy,
because early DWI/PI mismatch ("tissue at risk of infarction") indicates viable penumbral tissue.6–9 The aim of our study was to combine the information of stroke MRI sequences and IMZ-SPECT to follow the fate of reperfused mismatch tissue in patients with striatocapsular (SC) infarctions and large cortical hyperperfusion resulting from proximal middle cerebral artery occlusion.10 Hypoperfused tissue was defined with perfusion imaging; finally, infarcted tissue was defined by fluid-attenuated inversion recovery (FLAIR) sequence. We hypothesized that initially hypoperfused tissue on PI without infarction on the FLAIR sequence on day 7 is penumbral tissue that may show reduced IMZ uptake on SPECT as a consequence of a selective loss of cortical neurons after critical cortical hyperperfusion.

Patients and Methods

Patients and Inclusion Criteria
Within a period of 17 months, 86 patients with symptoms of acute ischemic stroke of the anterior cerebral territory were imaged with multiparametric MRI as part of a standardized imaging protocol within 6 hours after symptom onset. From this cohort, 12 consecutive patients met the following inclusion criteria: (1) successful completion of the stroke MRI protocol (see subsequently); (2) territorial perfusion deficit on PI; (3) striatocapsular infarction on the follow-up MRI (FLAIR, DWI) on day 7; and (4) feasibility of an IMZ-SPECT examination in the subacute stage (day 5 to 15). Three patients with a (complete) cortical infarction without a DWI/PI mismatch served as controls to consolidate the interpretation of the SPECT data. The local ethics committee approved the study, and informed consent was obtained.

Study Design
Stroke MRI was performed immediately after clinical evaluation and before possible intravenous thrombolysis with tissue plasminogen activator; MRI follow up was performed on days 1 and 7 and IMZ-SPECT on days 5 to 15.

Clinical Examination
At each time of scanning, the National Institute of Health Stroke Scale score was assessed by a stroke neurologist. Examination of aphasia was done using the Aachen Aphasia Bedside Test, which is validated for the acute phase after stroke;11 spatial neglect was examined using the letter cancellation test.12 More detailed neuropsychologic examinations were not performed in the acute and subacute phases after stroke.

Magnetic Resonance Imaging Protocol
MRI studies were performed on a 1.5-T clinical whole-body scanner (Magnetom Symphony/Sonata) with a standard head coil. The MRI protocol included an axial DWI sequence (3 b-values [0, 500, 1000 s/mm²], 20 slices, slice thickness=6 mm, interslice gap=0.6 mm), FLAIR sequence (20 slices, 6 mm, interslice gap=0.6 mm), MR angiography, and a PI sequence (30 to 42 repeated scans, bolus injection of gadolinium 6 seconds after the first scan, 11 to 20 slices, 5 mm, interslice gap 1.6 to 2 mm) resulting in a table time <20 minutes in most patients. Sequence parameters are described in detail elsewhere.13

Recanalization was assessed from the follow-up MRI study on days 1 and 7 on the basis of the PI and magnetic resonance angiography studies according to the modified Thrombolysis in Myocardial Infarction (TIMI) criteria for perfusion and vessel status (TIMI0=no recanalization; TIMI1=minimal recanalization/reperfusion [<20%], TIMI2= incomplete recanalization/reperfusion; TIMI3=complete recanalization/reperfusion).

Single-Photon Emission Computed Tomography Protocol
Before SPECT examination, perchlorate solution was given orally to block the thyroid gland. SPECT scans were started 5 minutes ("perfusion scan") and 90 minutes ("receptor scan") after injection of approximately 185 MBq [123I]-Iomazenil (Tyco Healthcare). A 4-head SPECT camera (Nuclide X-Ring/4R) specialized to brain imaging was used. One hundred twenty-eight projections (32 per head), each of 80 seconds duration, were recorded on a 64×64 matrix with a voxel size of 4.1×4.1×4.1 mm³. Thus, the total duration of each scan resulted in 43 minutes. Transaxial images were reconstructed iteratively using the ordered-subsets-expectation-maximization algorithm of the camera software (8 subsets, 2 iterations). Reconstructed images were postfiltered with a Butterworth filter (order=5, cutoff=20% of the Nyquist frequency). Spatial resolution of the final images was approximately 19 mm full width at half maximum. Attenuation correction was performed using Chang’s method with an attenuation coefficient of 0.12 cm⁻¹. Because SPECT images are commonly assumed to represent tracer uptake at the midscan time, the “receptor scan” represented IMZ uptake at approximately 112 minutes after injection of the tracer.

Postprocessing
Postprocessing of the MRI and SPECT images was performed offline with MR Vision (Menlo Park) and Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience) on a Linux workstation. The time to peak (TTP) parameter maps were computed from the PI data as described by Fiehler et al.14 FLAIR images of day 7 and the SPECT images were coregistered to the DWI (b=0) target images of day 0 with SPM2. DWI and PI had been performed consecutively within one imaging session; thus, coregistration of PI was guaranteed automatically. To compensate for differences in field of view, slice thickness, image matrix, and patients’ head orientation between the modalities, an affine stereotactical normalization, including translation, rotation, and spatial scaling, was performed to transform images into a standardized space (46 slices, voxel size 3×3×3 mm³). After normalization, MRI volumes of interest (VOIs), including the interpolated slices, were transferred to the corresponding SPECT image and mirrored to the unaffected hemisphere (Figure 1).

The normalized DWI (b=0) images of day 0 were segmented into cerebrospinal fluid, gray and white matter using the information of prior probability template images provided in SPM2.14 The resulting white matter mask was used to define the cortical rim of the SPECT images by cutting the white matter region from the SPECT images (“segmented SPECT,” SPECTseg=SPECT without white matter). Postprocessing, including coregistration and stereotactical normalization, was successful in all 15 subjects according to visual evaluation using the check-registration tool of SPM2.

Volumes of Interest and Analysis
Volumes of interest were defined on the stereotactically normalized images. In patients with striatocapsular infarction (SCI), the “TTP VOI” was defined by a TTP delay of >4 seconds compared with the corresponding area of the unaffected hemisphere (Figure 1). A delay of >4 seconds was used because it seems to correlate best with the acute clinical deficit.14 To define the “FLAIR VOI,” we first roughly delineated the infarction on the FLAIR image manually; within this delineation, the final infarction was defined automatically using a threshold >4×SD derived from the corresponding area in the unaffected hemisphere (Figure 1). The “mismatch VOI” was obtained by excluding the FLAIR lesion volume from the TTP lesion volume (VOI_mismatch=VOI_TTP−VOI_FLAIR). Thus, the mismatch VOI represented the brain tissue that was hypoperfused on PI but not infarcted on the outcome MRI. In the 3 patients with complete cortical infarctions, the VOI was defined to be identical with the FLAIR VOI. The “unaffected VOI” in SCI and cortical infarction was obtained by mirroring the respective “affected VOI” (VOI_mismatch=VOI_FLAIR) at the midsagittal plane. For evaluation of the SPECT
images, the VOIs were restricted to the cortical rim, i.e., the segmented SPECT image (segVOISPECT, see Figure 1).

Mean IMZ uptake was obtained by averaging IMZ uptake (count density) over all voxels within the restricted SPECT-VOI (segVOISPECT). The asymmetry ratio (AR) of the IMZ signal was obtained by dividing the mean IMZ uptake in the affected by the mean IMZ uptake in the unaffected VOI. Assuming (1) that IMZ kinetics were in some kind of equilibrium ("transient equilibrium") during the "receptor scan" and (2) that the nondisplaceable distribution volume of IMZ in brain tissue can be neglected compared with the specific distribution volume, the AR of the IMZ signal is proportional to the ratio of the mean BZ density in the respective VOIs. Although these assumptions might not be rigorously fulfilled, in particular in the mismatch VOI, the usefulness of the AR method has been demonstrated empirically by numerous groups.

The mean FLAIR signal intensity in the affected and unaffected VOIs (VOI_{mismatch}, VOI_{FLAIR}) was obtained by averaging the signal intensity over all voxels within the VOIs, respectively. The AR of the FLAIR signal was obtained by dividing the mean FLAIR signal in the affected by the mean FLAIR signal in the unaffected VOI. To test whether the mean of the IMZ and FLAIR ARs were significantly different from the population mean (assumed to be 1), we performed a one-sample $t$ test.

In a last step, we addressed the question whether there was a linear correlation of reduction in IMZ uptake and severity of hypoperfusion. To this end, we performed a Pearson’s correlation of the mean relative reduction of IMZ uptake (IMZ-AR) and the mean relative reduction of FLAIR uptake (FLAIR-AR).

**Results**

Demographic data, site of infarction, type of vessel occlusion, and clinical assessment of all 15 patients are displayed in Table 1; MRI and SPECT volumes as well as recanalization were superimposed to demonstrate the high homogeneity of the patient group.

Of the 15 patients with SCI treated by intravenous thrombolysis ($n=4$ within $\leq 3$ hours, $n=7$ within $\leq 6$ hours). On day 1, 6 patients showed no or only minimal reperfusion (TIMI 0 and 1) with a mean persistent TTP lesion of $62\pm 23$ mL; 6 patients showed incomplete (TIMI 2), mean persistent TTP lesion of $33\pm 15$ mL) or complete reperfusion (TIMI 3, without a persistent TTP lesion). After 7 days, patients 8 and 14 revealed prolonged hypoperfusion because of persistent artery occlusion; slight hypoperfusion in patients 4 and 9 was caused by internal carotid artery occlusion and subtotal internal carotid artery stenosis, respectively.

Eleven patients with SCI were treated by intravenous thrombolysis ($n=4$ within $\leq 3$ hours, $n=7$ within $\leq 6$ hours). On day 1, 6 patients showed no or only minimal reperfusion (TIMI 0 and 1) with a mean persistent TTP lesion of $62\pm 23$ mL; 6 patients showed incomplete (TIMI 2), mean persistent TTP lesion of $33\pm 15$ mL) or complete reperfusion (TIMI 3, without a persistent TTP lesion). After 7 days, patients 8 and 14 revealed prolonged hypoperfusion because of persistent artery occlusion; slight hypoperfusion in patients 4 and 9 was caused by internal carotid artery occlusion and subtotal internal carotid artery stenosis, respectively.

In the 12 patients with striatocapsular infarction, measurements of mean signal intensities in the FLAIR VOIs resulted in a mean FLAIR-AR of 1.844 (one-sample $t$ test, 2-sided, $P<0.05$); measurement of the mean IMZ uptake in the restricted FLAIR VOI resulted in a clearly reduced IMZ-AR of 0.854 ($P<0.05$), demonstrating the validity of our IMZ-SPECT methodology.

In the 12 patients with striatocapsular infarction, measurement of mean signal intensity in the mismatch VOI resulted in a normal FLAIR-AR of 1.009 ($P=0.3$), whereas measurement of mean IMZ uptake in the restricted mismatch VOI revealed a mean IMZ-AR of 0.849 ($P<0.05$, see Table 2, Figure 2). Patients without/minimal recanalization on day 1 (TIMI 0/1) showed clearly reduced (patients 8, 6, and 13), slightly reduced (patient 10) as well as normal (patients 14 and 5) IMZ-ARs (Table 2). Figure 3 shows one patient with a complete cortical infarction and 2 patients with striatocapsular infarction with and without reduced cortical IMZ uptake. As expected, correlation analysis of relative TTP delay (TTP-AR) and degree of incomplete infarction (IMZ-AR) revealed a negative correlation; however, the correlation was weak ($r=-0.25$) and not statistically significant ($P>0.05$).

**Discussion**

The identification of tissue at risk of infarction by multimodal stroke MRI allows to select patients with acute stroke likely to benefit from thrombolysis in an extended time window. If successful vessel recanalization results in salvage of mismatch tissue without a signal hyperintensity on FLAIR imaging during follow up, it is usually assumed that the tissue is intact. We have shown for the first time that incomplete...
infarction occurs in cortical mismatch tissue of patients with striatocapsular infarctions. This incomplete infarction remained undiscovered on MRI data and must be considered as a further graduation of the fate of “mismatch tissue” after vessel occlusion together with hemorrhagic transformation, complete infarction, and complete tissue salvage.

The degree of incomplete infarction showed a continuum of clearly reduced to normal IMZ ARs in the mismatch VOIs that were characterized by normal FLAIR signal intensity. Patients without or with only minimal recanalization on day 1 (TIMI 0/1) showed clearly reduced (patients 8, 6, and 13), slightly reduced (patient 10) as well as normal (patients 14 and 5) IMZ-ARs. Thus, reperfusion characteristics 1 day after the stroke did not differ in patients with low and normal IMZ as asymmetry ratios. This supports the notion that besides the time point of reperfusion, a sufficient collateral blood supply is a crucial parameter for survival of cortical neurons after vessel occlusion.

We defined the hypoperfused tissue on PI-derived TTP maps with a relative TTP delay of \( \frac{4}{H} \) seconds compared with the healthy hemisphere. We used a TTP delay of \( \frac{4}{H} \) seconds because it was demonstrated that this value correlates best with clinical impairment. Time-dependent perfusion thresholds have first been established by positron emission tomography with \( ^{15} \text{O}-\text{water} \) to distinguish hypoperfused tissue evolving toward infarction (<12 mL/min per 100 g) from penumbral flow with functionally compromised but viable tissue (12 to 20 mL/min per 100 g). In a comparison of positron emission tomography and MRI perfusion data, the best estimate of penumbral flow (20 mL/min per 100 g) was found for a TTP delay of \( \frac{4}{H} \) seconds. However, recent data suggest that, at least in patients with hemodynamic infarction, this threshold may include tissue with only modest hemodynamic compromise. Thus, TTP maps with a delay of \( \frac{4}{H} \) seconds may still tend to overestimate the true extent of the “tissue at risk.” This might be one reason for the lower effects in our study with ARs of 0.89 to 1.01 (mean, 0.95) in SCI compared with Nakagawara and colleagues who reported IMZ-ARs of 0.64 to 1.01 (mean, 0.89) in areas of reperfused noninfarcted cortex. One crucial point in comparing the ARs is the definition of the VOIs. Nakagawara and colleagues divided the reperfused, noninfarcted areas in arbitrary subregions, which were more or less affected; thus, they found a broader range of ARs in their study. Our VOIs were predefined by the extent of hypoperfusion; thus, IMZ-ARs reflected an average value of the whole VOI, including more and less affected tissue. Furthermore, we strictly excluded regions that showed an infarction on the MRI data; even small cortical lesions

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Mean (SD) 62 (2) 13.2 (4.2) 9.3 (4.9) 7.3 (6.7) 1.0 1.0 1.0 210 280 305 120 205 (68)

L indicates left; R, right; SC, striatocapsular; NIHSS, National Institute of Health Stroke Scale; IV, intravenous; min, minutes after symptom onset; MCA, middle cerebral artery; trif, trifurcation; ICA, internal carotid artery; CTO, occlusion of the carotid T.
only visible on diffusion-weighted imaging were excluded. Consequently, the FLAIR-ARs showed no difference between the affected and unaffected hemisphere, which demonstrated that the cortical tissue was inconspicuous on MRI.

Eight of 12 patients with SC infarcts initially presented with cortical symptoms like aphasia or neglect as detected with the Aachen Aphasia Bedside Test and letter cancellation test. Only 2 patients showed persistent aphasia after 7 days. These 2 patients displayed the lowest IMZ-ARs of all patients with SC infarction. Hillis and colleagues24 showed that aphasia after subcortical infarction improved after cortical reperfusion. The same was demonstrated by Karnath et al25 who showed that neglect in patients with basal ganglia infarction was only present in patients with initial cortical hypoperfusion. Weiller et al26 demonstrated a significantly decreased regional cerebral blood flow in the cortical middle cerebral artery territory with corresponding focal cortical atrophy on MRI 1 year after SC infarction only in patients with neglect or aphasia. They concluded that aphasia or neglect after SC infarcts are most likely attributable to selective neuronal loss of the cerebral cortex resulting from prolonged middle cerebral artery occlusion and insufficient

Figure 2. Plots of AR. Asymmetry ratios for iomazenil uptake on SPECT and signal intensity on FLAIR images of day 7 are displayed. Although FLAIR-AR are high for patients with cortical infarctions and normal in all patients with striatocapsular infarctions, IMZ-ARs are distributed continuously from complete to incomplete infarction up to normal tissue.
collateral blood flow. However, at this time, IMZ-SPECT or flumazenil positron emission tomography was not yet available to prove the hypothesis. Summarizing these results and our observations, cortical hypoperfusion causes a functional disruption of cortical networks. In some cases for which a more severe hypoperfusion (although of short duration) must be assumed, additional destruction of more or less cortical neurons occurs. The latter may be an explanation for the observation that after reperfusion, functional restitution may occur delayed.27 However, if SCI did not cause a severe deficit attributable to infarction of the internal capsule, prognosis for SCI with complete functional recovery seems to be good despite (partial) incomplete cortical infarction.

Finally, some methodological issues have to be addressed. There has been a long discussion about the optimal scan time for imaging central benzodiazepine receptors with a static IMZ-SPECT scan. This extensive discussion was fueled by the lack of a clearly defined optimal scanning time. In fact, IMZ-SPECT scans yield essentially the same information about the availability of central benzodiazepine receptors in a rather large time window. For example, Busatto et al reported that the estimate of the specific-to-nonspecific partition coefficient $V_s$, a measure often used to quantify the receptor availability in single scan approaches,19 reached a plateau from 60 to 75 minutes after injection onward.28 Concerning effects of cerebral blood flow, computer simulations performed by Onishi et al suggested that IMZ-SPECT images are least affected by cerebral blood flow at approximately 180 minutes postinjection.29 Simulated count ratios at 180 minutes reproduced the true distribution volume ratio with a mean error of 3.6% when perfusion was varied between 60% and 120% of the baseline value. Count ratios at 110 minutes postinjection reproduced the true distribution volume ratio with a mean error below 15%, which still appears acceptable. Advantages of “early delayed” scanning at 110 minutes postinjection30,31 compared with “late delayed” scanning at 180 minutes include (1) better compliance/acceptance by the patient/referring physician and (2) improved count statistics (the peak of IMZ concentration at 20 to 30 minutes postinjection is followed by a decrease of IMZ concentration of approximately 15% per hour32).

In conclusion, using IMZ-SPECT, we demonstrated a selective loss of cortical neurons in patients with striatocapsular infarctions, namely in tissue that showed preceding hypoperfusion in PI-derived TTP maps but was inconspicuous on follow-up FLAIR images. This study is an extension to previous MRI stroke studies because the application of IMZ-SPECT offers the opportunity to examine the integrity of cortical neurons after hypoperfusion. Incomplete infarction of MR-defined mismatch tissue should be considered as a further graduation of tissue fate after vessel occlusion besides complete salvage and complete infarction.

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**Disclosures**

None.
References

Iomazenil-Single-Photon Emission Computed Tomography Reveals Selective Neuronal Loss in Magnetic Resonance-Defined Mismatch Areas
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