

# Mechanism of Reduction of Cortical Blood Flow in Striatocapsular Infarction: Studies Using [<sup>123</sup>I]Iomazenil SPECT

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**Single photon emission computed tomography (SPECT) using [<sup>123</sup>I]iomazenil (radioligand of central-type benzodiazepine receptors) was employed to examine two patients with striatocapsular infarction. Patient 1 was a 61-year-old female with motor aphasia and hemiplegia on the right side. Magnetic resonance imaging (MRI) showed a lesion in the anterior limb of internal capsule and putamen on the left side. SPECT using <sup>99m</sup>Tc-HMPAO revealed a reduction of cerebral blood flow (CBF) in the frontoparietal region on the left side, but the delayed images in SPECT using [<sup>123</sup>I]iomazenil showed only a mild decrease of accumulation in the frontal lobe. Patient 2 was a 55-year-old male with hemiplegia on the left side. MRI showed a lesion localized in the basal ganglia and posterior limb of the internal capsule on the right side. SPECT using <sup>99m</sup>Tc-HMPAO revealed a reduction of CBF in the frontoparietal region on the right side and in the cerebellar hemisphere on the left side, but the delayed images in SPECT using [<sup>123</sup>I]iomazenil showed little decrease of accumulation in parietal lobe. The discrepancy between CBF and receptor images suggested that cortical hypoperfusion on striatocapsular infarction might reflect hypometabolism due to disconnection of the neuronal network between subcortical structure and cortex.** © 1997 Academic Press

## INTRODUCTION

Striatocapsular infarction (SCI) is frequently associated with higher cortical dysfunction (Bladin and Berkovic, 1984). Although the lesions of SCI are restricted to basal ganglia and internal capsule, studies of cerebral blood flow using single photon emission computed tomography (SPECT) in patients with SCI have revealed hypoperfusion in both basal ganglia and cerebral cortex (Skyhoj *et al.*, 1986; Perani *et al.*, 1987; Vallar *et al.*, 1988; Weiller *et al.*, 1990). The mechanism

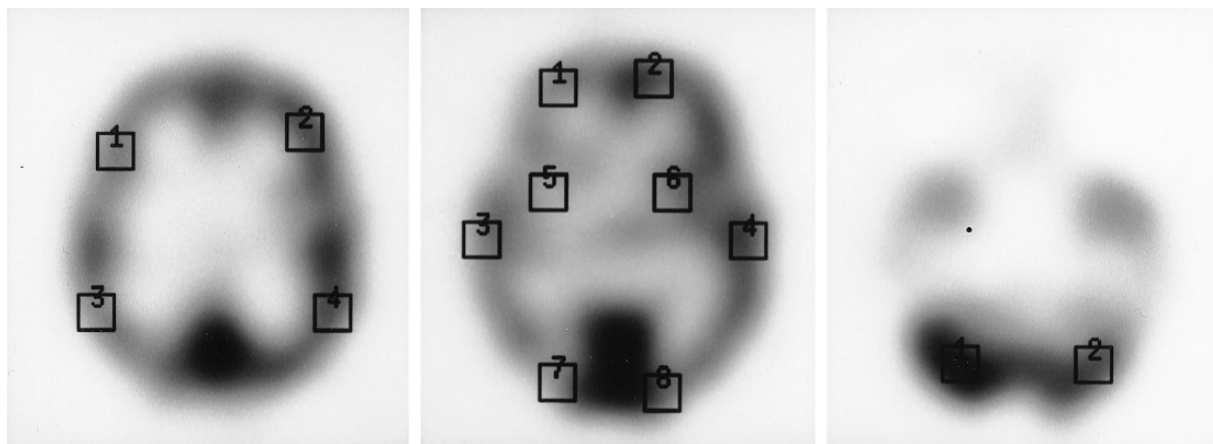
of cerebral blood flow (CBF) reduction in the cortex in SCI was suggested to be stenosis of the middle cerebral artery (MCA) (Skyhoj *et al.*, 1986; Weiller *et al.*, 1990) or disconnection of neuronal networks between the subcortical structure and cortex (Perani *et al.*, 1987; Vallar *et al.*, 1988). However, there was no direct evidence supporting the latter hypothesis because of methodological limitations. Recently, a radioligand for the central type of benzodiazepine receptor (BZR) has been developed for SPECT examination (Beer *et al.*, 1988). Clinical trials of this ligand in patients with epilepsy (Schubiger *et al.*, 1991), degenerative disease (Schubiger *et al.*, 1991), and cerebral infarction (Hatazawa *et al.*, 1995) showed that it is a useful tracer for detection of neuronal cell damage. To clarify the mechanism of the reduction of CBF in the cerebral cortex in patients with SCI, we performed SPECT examinations using [<sup>123</sup>I]ethyl-7-iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1.5- $\alpha$ ]-1,4-benzodiazepine-3-carboxylate [<sup>123</sup>I]iomazenil) and technetium-99m hexamethylpropylene amine oxime (<sup>99m</sup>Tc-HMPAO).

## MATERIALS AND METHODS

SPECT studies were performed on two patients with SCI. Magnetic resonance imaging (MRI) examination in patient 1 was performed on a Gyroscan-1.5 T (Philips, Eindhoven, The Netherlands); T<sub>1</sub>-weighted (TR 425 ms, TE 12 ms) and T<sub>2</sub>-weighted (TR 3000 ms, TE 90 ms) images were obtained. MRI in patient 2 was performed with a Magnetom-1.0 T (Siemens, Erlangen, Germany); T<sub>1</sub>-weighted (TR 500 ms, TE 15 ms) and T<sub>2</sub>-weighted (TR 3000 ms, TE 90 ms) images were obtained.

SPECT was performed by using a rotating gamma camera (GCA-901A, Toshiba, Japan; matrix of collection, 64 × 64; full width at half maximum, 15 mm) with a standard collimator. Data were prefiltered with a Winer filter and reconstructed with a Ramp filter. Reconstructed images were corrected by using Chang's attenuation correction, with an attenuation coefficient of 0.08 cm<sup>-1</sup>. Scatter correction was not done. SPECT

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**FIG. 1.** The locations of the ROI in the brain. ROI were located symmetrically in 12 or 14 regions, including lateral frontal, frontal, parietal, temporal, occipital, basal ganglia, and cerebellum.

images were obtained in 15 consecutive axial slices every 8 mm, parallel to and above the orbitomeatal line. The regions of interest (ROI) (of  $4 \times 4$  pixels; pixel size, 4 mm) were 12 or 14 symmetrically located regions in the lateral frontal, frontal, parietal, temporal, and occipital areas; basal ganglia; and cerebellar hemisphere, based on 3 axial slices (Fig. 1). On delayed images with iomazenil, the ROI in basal ganglia were not located because there was little accumulation in these regions, reflecting the distribution of BZR in the brain (Woods *et al.*, 1992). The extent of change of CBF or binding of BZR, expressed as uptake ratio of radioligand on the affected side to that on the unaffected side, was calculated in the selected brain regions. SPECT examination of CBF was conducted by intravenous injection of  $^{99m}\text{Tc}$ -HMPAO (740 MBq); data collection was started 5 min after injection and continued for 20 min. SPECT imaging of BZR was done with  $^{123}\text{I}$ iomazenil (167 MBq; Medipysics, Japan). Early image scans were started 5 min after intravenous injection of  $^{123}\text{I}$ iomazenil and data were collected for 20 min. Delayed image scans were started 165 min after injection, and data were collected for 30 min. This study was performed after the patients had given their informed consent and with the approval of the ethics committee of our hospital.

## PATIENTS

### Patient 1

A 61-year-old female was admitted to our hospital with aphasia and hemiplegia on the right side. Neurological examinations revealed motor aphasia of the Broca type, hemiplegia, sensory impairments and pathological reflexes on the right side. Higher cortical dysfunction other than motor aphasia was not recognized. Chest X ray showed moderate cardiomegaly and ECG

revealed atrial fibrillation. Her common and internal carotid arteries showed no abnormalities on ultrasonography.  $T_1$ -weighted MRI images taken on the 10th day after onset revealed low signal intensities in the anterior limb of the internal capsule and putamen on the left side, while  $T_2$ -weighted images revealed high signal intensities in these regions (Fig. 2). SPECT using  $^{99m}\text{Tc}$ -HMPAO on the 6th day after onset showed a decrease of CBF in bilateral hemispheres, especially in the frontal region on the left side (Fig. 3, top). Early SPECT images using  $^{123}\text{I}$ iomazenil on the 13th day after onset showed a decrease of accumulation in basal ganglia and frontotemporal regions on the left side and cerebellum on the right side (Fig. 3, middle), while delayed images showed a slight decrease of accumulation in the frontal region on the left side (Fig. 3, bottom). Uptake ratios in CBF images and in early images of iomazenil were low compared with those in other regions, not only in the basal ganglia, but also in the frontal, temporal, and parietal regions, but uptake in delayed images in these regions showed little difference from the contralateral side (Table 1).

### Patient 2

A 55-year-old male developed hemiparesis on the left side. This gradually worsened, and he developed dysarthria on the evening of onset. Neurological examinations showed a confused state, sensory impairments, hemiplegia, hyperreflexia, and pathological reflexes on the left side. Laboratory examination showed hypercholesterolemia, increase of serum glucose concentration, and mild polycythemia.  $T_1$ -weighted MRI images on the 10th day after onset showed low signal intensities in the putamen and posterior limb of the internal capsule on the right side, and these lesions were seen as high signal intensities on  $T_2$ -weighted images (Fig. 4). MR angiography on the 13th day showed a deficit in the  $M_1$

portion of the middle cerebral artery on the right side, and SPECT using <sup>99m</sup>Tc-HMPAO on the 11th day showed hypoperfusion in the frontal, parietal, and temporal regions on the right side and cerebellar hemisphere on the left side (Fig. 5, top). Early images using [<sup>123</sup>I]iomazenil showed a severe decrease of accumulation in the basal ganglia and a mild decrease in the frontal, temporal, and occipital regions on the right side and cerebellar hemisphere on the left side (Fig. 5, middle), though delayed images showed a slight decrease of accumulation in right parietal region (Fig. 5, bottom). Uptake ratios in CBF images and in early images of benzodiazepine receptors in the cerebral hemisphere tended to be low, excluding that in the cerebellum, but uptake in delayed images in these regions showed little difference from the contralateral side (Table 1).

## DISCUSSION

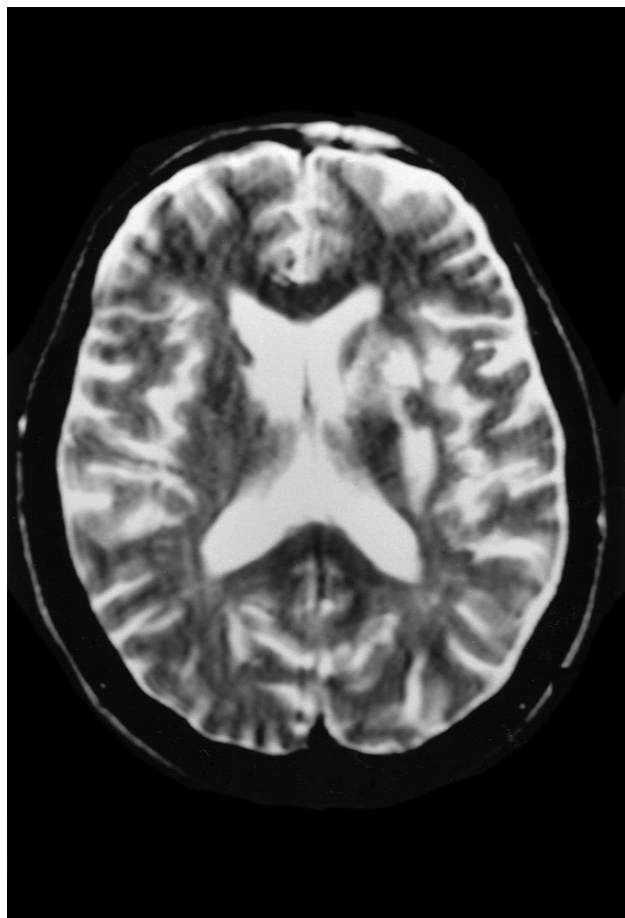
The diagnosis of SCI was based on clinical manifestations and CT or MRI identification of a lesion localized

in the basal ganglia and internal capsule with a maximum diameter of 3.0 cm or more (Bladin and Berkovic, 1984). The etiology of SCI is usually cardiogenic embolism (Weiller *et al.*, 1990; Donnan *et al.*, 1991), but severe stenosis or obstruction of the internal carotid artery or a proximal segment of the middle cerebral artery has been reported in some cases with SCI (Weiller *et al.*, 1990; Donnan *et al.*, 1991). There are several reports which demonstrate a reduction of CBF in the cerebral cortex in addition to basal ganglia in patients with SCI (Skyhoj *et al.*, 1986; Perani *et al.*, 1987; Vallar *et al.*, 1988; Weiller *et al.*, 1990). Weiller *et al.* (1990) reported that reduction of CBF in these regions can be explained by stenosis of major vessels, based on the findings of angiography, and they afterward asserted that it is most likely due to selective neuronal loss of the cerebral cortex due to prolonged MCA occlusion (Weiller *et al.*, 1993).

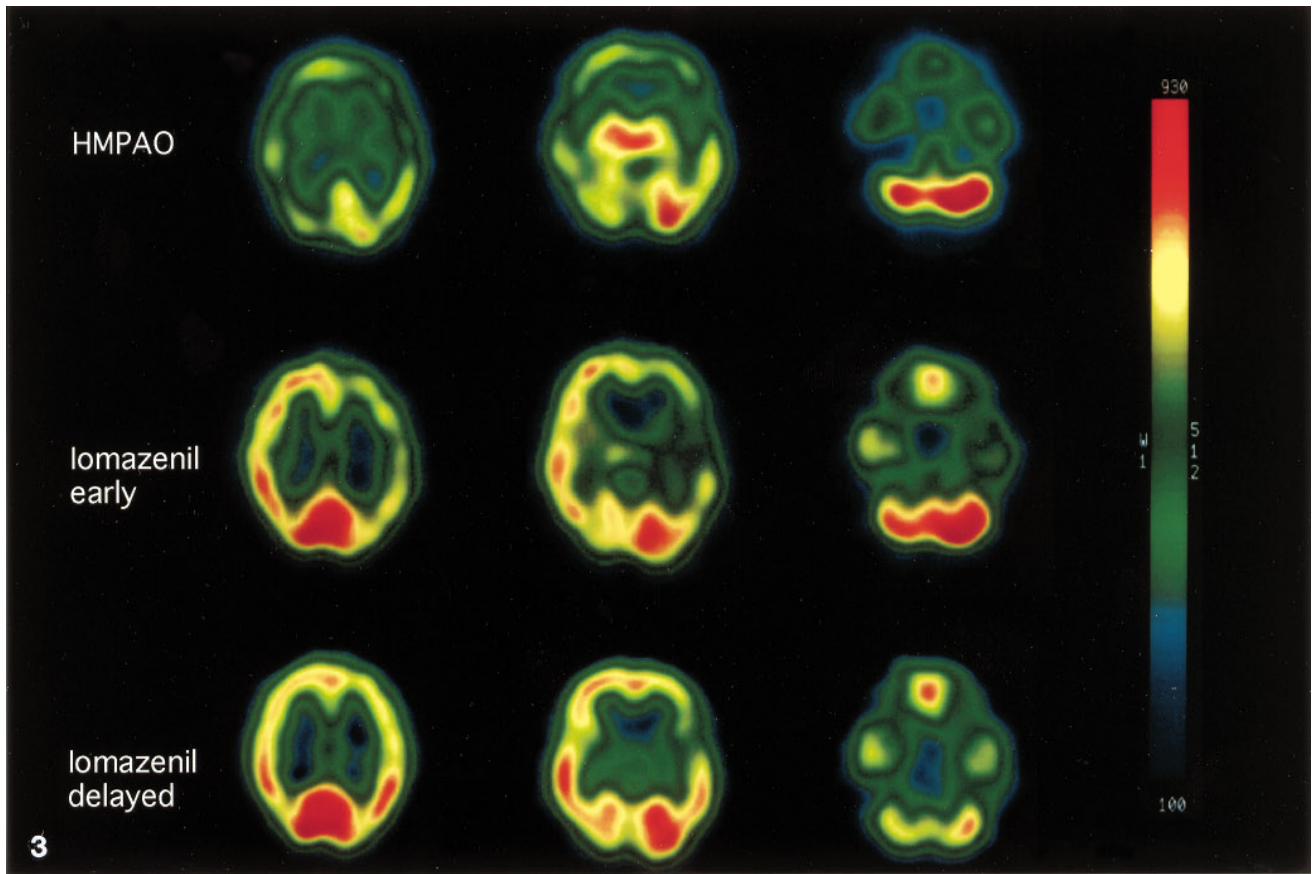
However, we (Meyer *et al.*, 1970) and others (Baron *et al.*, 1980) reported a reduction of CBF probably due to a reduction of cerebral metabolism, in an area remote from the lesion in acute CVD, and explained it in terms of diaschisis. Perani *et al.* (1987) speculated that the reduction of CBF observed in SCI is a reflection of hypometabolism in cerebral cortex due to disconnection between subcortical structures and cerebral cortex, in accordance with the concept of diaschisis. Vallar *et al.* (1988) supported the latter hypothesis on the basis of SPECT studies in patients with subcortical cerebrovascular diseases, including SCI.

Although CBF images obtained by SPECT using <sup>99m</sup>Tc-HMPAO in the present patients revealed hypoperfusion in cortical regions of the side with infarction, regions in the basal ganglia did not show a decrease of CBF. SPECT using HMPAO in our patients was performed in the subacute stage of infarction, on the 6th and the 11th day after onset, respectively. Sperling *et al.* (1993) reported that the estimation of CBF by SPECT using HMPAO in subacute ischemic stroke might give erroneously high values due to focal hyperfixation of HMPAO. The poor delineation of CBF to the infarct area in basal ganglia in the present study might reflect this characteristic of HMPAO.

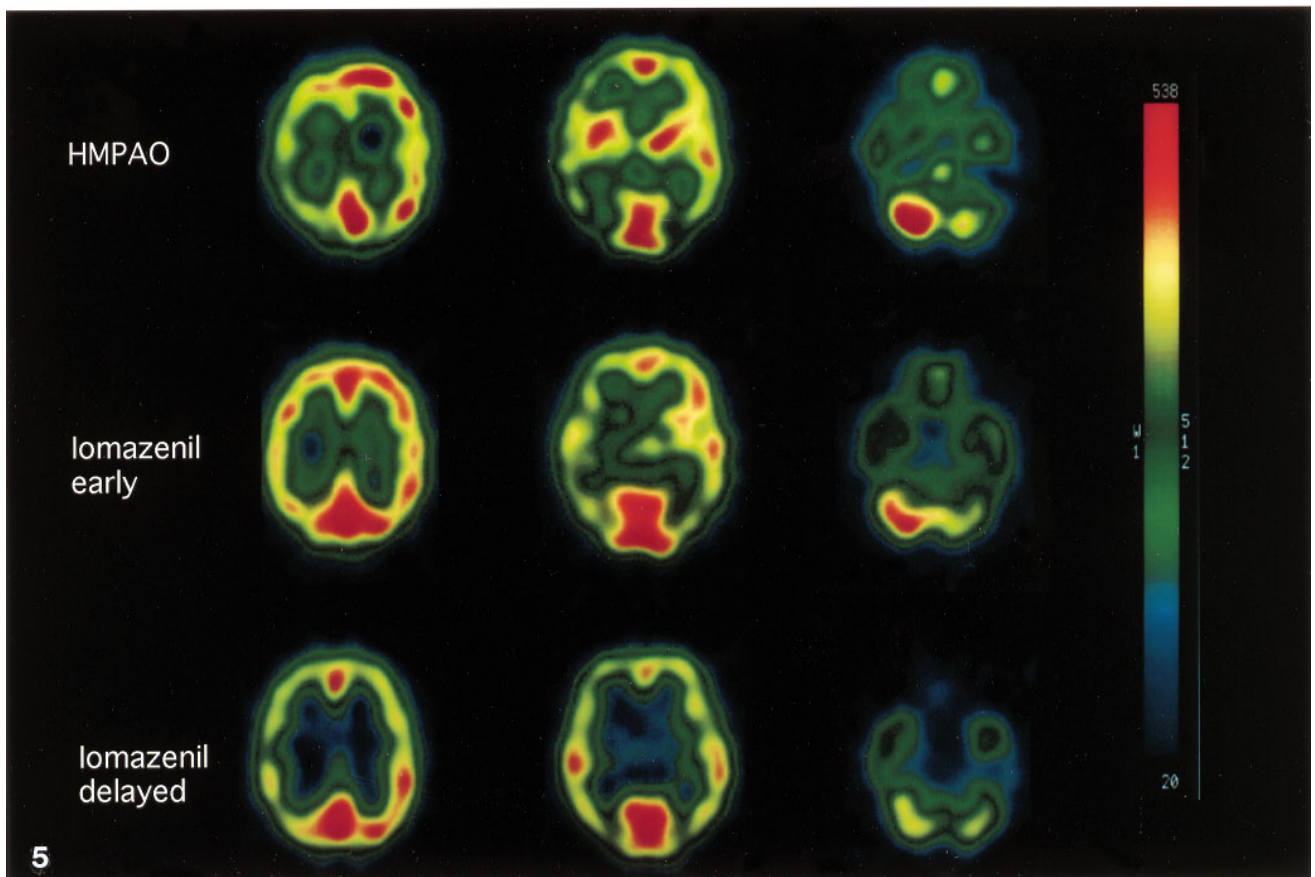
Recently, a radioligand for human BZR has been developed for use in SPECT studies (Beer *et al.*, 1988). BZR are classified into two types, central and peripheral (Souza *et al.*, 1985); the central type is expressed on neuronal cells and the peripheral type on glial cells (Souza *et al.*, 1985). This radioligand, iomazenil (Ro16-0154), has a high affinity for central-type BZR and is characterized by a high ratio of specific to nonspecific binding (Beer *et al.*, 1990). When SPECT is performed using [<sup>123</sup>I]iomazenil, the early image scanned from 5 min after intravenous administration is determined mainly by the cerebral blood flow (Woods *et al.*, 1992), but the delayed image from 120 min after administra-



**FIG. 2.** T2-weighted MRI imaging on the 10th day after onset of cerebral infarction in patient 1. High signal intensity is seen in the anterior limb of the internal capsule and basal ganglia on the left side. The right side of these images represents the left side in the patients.



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TABLE 1

Uptake Ratios of Affected Side to Unaffected Side in CBF Images Obtained with HMPAO and Early and Delayed Images with Iomazenil

ROI	HMPAO	Iomazenil (early)	Iomazenil (delayed)
Patient 1			
Lateral frontal	0.92	0.90	0.96
Frontal	0.93	0.94	0.95
Parietal	0.98	0.93	0.98
Temporal	1.05	0.78	0.93
Occipital	1.10	1.10	1.05
Basal ganglia	0.91	0.83	—
Cerebellum	1.09	1.07	1.02
Patient 2			
Lateral frontal	0.88	0.87	0.96
Frontal	0.88	0.82	0.95
Parietal	0.86	0.84	0.93
Temporal	0.87	0.78	1.03
Occipital	0.88	0.90	0.93
Basal ganglia	1.11	0.80	—
Cerebellum	1.37	1.20	1.10

tion reflects the distribution of BZR in the brain (Woods *et al.*, 1992). This delayed image reveals a higher accumulation in cerebral cortex and cerebellar cortex than in white matter, striatum, and thalamus, reflecting the distribution of BZR in the brain (Woods *et al.*, 1992).

In our present studies, delayed images in cortical regions of SCI demonstrated little decrease of accumulation, although the CBF image obtained by SPECT using <sup>99m</sup>Tc-HMPAO revealed an obvious reduction of CBF. Since the delayed images of SPECT using [<sup>123</sup>I]iomazenil reflect the density and the binding ability of BZR in neuronal cells (Woods *et al.*, 1992), this phenomenon could be accounted for by the hypothesis that most of the neuronal cells in cortical regions that show a decrease of CBF survive or at least retain their membrane structures. Sette *et al.* reported that the brain benzodiazepine receptors were preserved in periinfarcted cortical areas after ischemia, although these areas revealed hypometabolism by positron emission tomography in an animal model (Sette *et al.*, 1993). Their report is consistent with the above consider-

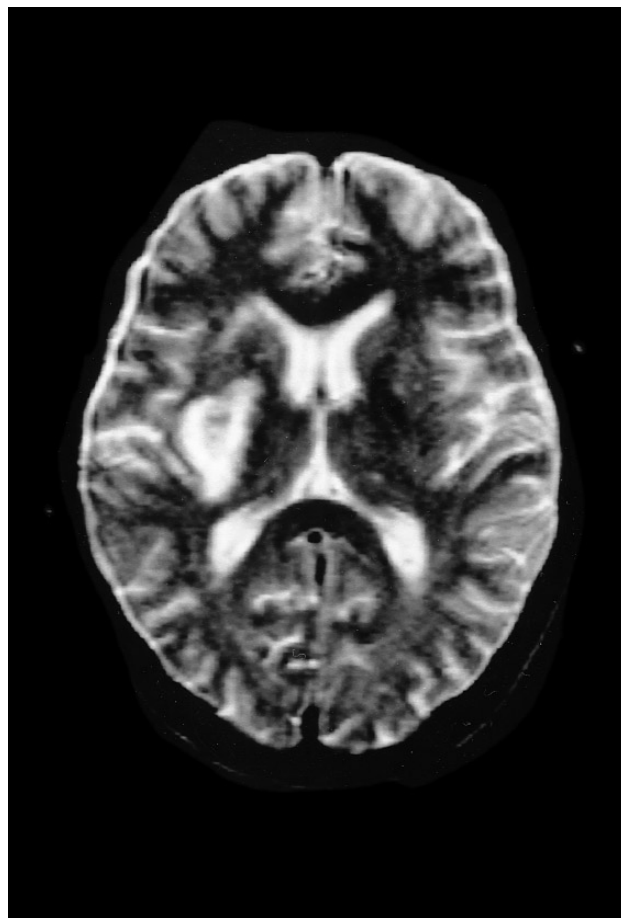


FIG. 4. T2-weighted MRI imaging in patient 2 on the 10th day after onset of cerebral infarction. High signal intensity is seen in the basal ganglia and the posterior limb of the internal capsule on the right side.

ations. In patient 2 in the present study, MR angiography showed a deficit in the middle cerebral artery on the infarcted side. As the mechanism of a decrease of cortical flow in this patient, the possibility of occlusion or stenosis of the MCA cannot be rejected. But since the delayed images of iomazenil in this patient certified that most of the neuronal cells in the cortical regions were preserved, it is speculated that a decrease of CBF in the cortical regions in this patient was associated with hypometabolism in these regions rather than

FIG. 3. SPECT imaging in patient 1. Imaging using <sup>99m</sup>Tc-HMPAO (top) was performed on the 6th day after onset of cerebral infarction. Hypoperfusion is apparent in the bilateral hemispheres, especially in the frontal region on the left side. Early images using [<sup>123</sup>I]iomazenil (middle) on the 21st day after onset revealed a decrease in the frontotemporal and basal ganglial regions on the left side. Delayed images 3 h after injection of [<sup>123</sup>I]iomazenil demonstrated a mild decrease of accumulation in the lateral region of frontal lobe on the left side (bottom).

FIG. 5. SPECT images in patient 2. Imaging using <sup>99m</sup>Tc-HMPAO (top) revealed hypoperfusion in the right frontal, parietal, and temporal regions and left cerebellar hemisphere. Early images using [<sup>123</sup>I]iomazenil showed decreased accumulation in the frontal; parietal, temporal, and basal ganglial regions on the right side and cerebellar hemisphere on the left side (middle), but delayed images showed a slight decrease of accumulation in right parietal region (bottom).

direct ischemic damage in the neuronal cells of the cortex by occlusion or severe stenosis of the MCA.

Although the possibility remains that the ischemic event induces hyperexpression of BZR in neuronal cells, or the incomplete infarction in the cortex by prolonged obstruction of the MCA, it seems more likely that the disconnection of neuronal networks, that is, diaschisis, plays the main role in causing the decrease of CBF in cortex of patients with SCI.

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