Cerebral Infarction within Six Hours of Onset: Prediction of Completed Infarction with Technetium-99m-HMPAO SPECT

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Technetium-99m-HMPAO can be used to evaluate abnormal brain perfusion in the hyperacute stage of stroke. **Methods:** We investigated cerebral blood flow using ^{99m}Tc-HMPAO SPECT in 31 patients within 6 hr after the onset of cerebral infarction and analyzed the relationship between abnormal perfusion and morphological changes on follow-up CT scans. Patients were classified into an infarct group and a noninfarct group, and the lesions on SPECT images were divided into infarct and peri-infarct regions. **Results:** Among a total of 30 infarct regions, three lesions studied at 1.5, 2.5 and 5 hr after the ictus showed local hyperperfusion suggestive of early postischemic hyperemia, while the other 27 lesions demonstrated local hypoperfusion. All of the peri-infarct regions showed moderate hypoperfusion. The noninfarct group consisted of five patients, four of whom showed no perfusion abnormalities. The lesion-to-contralateral radioactivity ratios for the infarct and peri-infarct regions were respectively 0.48 ± 0.14 and 0.75 ± 0.10 in the patients with hypoperfusion, while the right-to-left ratio in the noninfarct group was 0.97 ± 0.10. **Conclusion:** This SPECT study of cerebral blood flow demonstrates that local hyperperfusion occurs in some infarcts even within 6 hr of onset and that infarcted and morphological viable brain can be distinguished by a lesion-to-contralateral radioactivity ratio of 0.6 within this time range.

Key Words: cerebral infarction, SPECT, technetium-99m-HMPAO, cerebral blood flow

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The ischemic threshold is one of the intriguing concepts in the management of cerebral infarction. Some of the therapeutic interventions for chronic cerebral infarction, i.e., anastomotic bypass surgery and carotid endarterectomy, are based on the concept that improving blood flow to oligemic brain tissue can normalize the imbalance between blood supply and metabolism (*1–2*). Similarly, the intravenous or intra-arterial injection of thrombolytic agents soon after vascular occlusion in acute cerebral ischemia is performed on the same basis. However, determination of the ischemic threshold has been dependent upon data obtained in experimental studies of uniform occlusion models or the clinical investigation of patients with subacute or chronic cerebral infarction (*2–6*).

Although it has been difficult to estimate the flow threshold in the acute stage of cerebral ischemia in the clinical setting, a new radiopharmaceutical agent for SPECT imaging, ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO), has facilitated emergency hemodynamic studies and made the rapid semiquantitative evaluation of cerebral blood flow (CBF) possible. The twin purposes of the present study are to investigate CBF abnormalities by SPECT within 6 hr after the onset of cerebral ischemia and to use CBF to determine the CBF threshold for the survival of brain tissue. The CBF threshold in the present study is defined as the critical value for the morphological change with referring CT images. A retrospective clinical analysis was performed with the aim of providing useful information for the early prediction of completed cerebral infarction.

SUBJECTS AND METHODS

Subjects

Thirty-one patients (age 39–86 years; 14 women and 17 men) who were clinically diagnosed as having supratentorial infarction were analyzed on admission. Neurological examination was performed. (A clinical profile of the patients is presented in Table 1.) The major deficits on admission were hemiparesis in 27 patients, aphasia in two patients and disorientation in two patients. All patients had a sudden onset of symptoms and the time of onset was determined by reliable information obtained from the patients themselves or their relatives. Cerebral embolism, defined as the finding of atrial fibrillation on the admission electrocardiogram and/or emboli in the main intracranial arteries seen on the initial cerebral angiogram (*7–8*), was observed in 21 of 31 patients. Computed tomography (CT) was performed on admission in order to rule out intracranial hemorrhage. Patients with lacunar and infratentorial infarction were retrospectively excluded by the findings on follow-up CT and/or magnetic resonance imaging (MRI).

SPECT Procedure

A Headtome II or SET 080 SPECT system (Shimazu Co., Kyoto, Japan) was used for CBF imaging. The Headtome II is a

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TABLE 1
Clinical Profile of the Subjects

Subject no.	Age/Sex	SPECT examination time after onset (hr)	Angiographic finding on admission	LDA on Follow-up CT	Type of interventional therapy	Reperfusion
1	60/M	1.5	ACA branch occlusion with blush	Cor, Cor	None	Partial
2	66/M	1.5	None	N	None	Unknown
3	59/M	1.6	MCA occlusion	Cor	None	Unknown
4	62/F	1.7	ICA occlusion	Cor	Intra-arterial	No reperfusion
5	74/F	1.7	ICA occlusion	Cor	Intra-arterial	Partial
6	80/F	1.8	ACA and MCA branch occlusion	Cor	None	Unknown
7	65/F	1.8	MCA occlusion	Cor	None	Unknown
8	46/F	2.0	MCA branch occlusion	Cor	Intra-arterial	No reperfusion
9	66/F	2.0	MCA occlusion	Cor	Intra-arterial	Partial
10	56/M	2.0	ACA occlusion	Cor, Cor	None	Unknown
11	76/M	2.2	MCA and ACA branch occlusion	Cor, Cor	None	Unknown
12	75/M	2.3	MCA branch occlusion	Cor	None	Unknown
13	74/F	2.3	MCA occlusion	Cor	Intra-arterial	Partial
14	76/F	2.4	blush only	Cor	None	Complete
15	86/M	2.5	None	Cor	None	Unknown
16	69/M	2.8	MCA occlusion	WM	None	Unknown
17	65/F	2.8	MCA occlusion	N	Intra-arterial	Complete
18	72/F	3.0	ICA occlusion	Cor—WM	None	Unknown
19	82/F	3.2	MCA occlusion	Cor	Intra-arterial	Partial
20	70/M	3.2	ICA occlusion	Cor	None	Unknown
21	66/M	3.7	MCA branch occlusion	Cor	None	Unknown
22	73/M	3.7	ICA occlusion	Cor—WM	None	Unknown
23	39/M	4.0	None	N	None	Unknown
24	59/M	4.0	MCA branch occlusion	Cor	Intra-arterial	No reperfusion
25	77/M	4.1	None	N	None	Unknown
26	63/M	4.6	None	Cor	None	Unknown
27	59/F	4.7	None	Cor, Cor	None	Unknown
28	53/M	5.2	None	WM	None	Unknown
29	68/F	5.3	None	N	None	Unknown
30	74/F	5.4	None	Cor, WM	None	Unknown
31	67/M	5.7	ICA occlusion	Cor—WM	None	Unknown

ACA = anterior cerebral artery; MCA = middle cerebral artery; ICA = internal cerebral artery; LDA = low density area; Cor = cortex; WM = white matter; and N = normodensity.

three-ring scanner that obtains six to nine slices of 17 mm in thickness with a 35-mm interslice gap and has a high-resolution (HR) collimator. The in-plane and z-direction spatial resolution were respectively 11 mm and 17 mm with FWHMs. The SET 080 is a continuous cylindrical ring scanner that obtains 32 tomographic transaxial slices. Using a HR collimator, the slice thickness was set at 23 mm with no interslice gap. The in-plane and z-direction spatial resolution were respectively 11 mm and 18 mm with FWHMs. SPECT data acquisition time was 27 min on average, and the raw data obtained by both SPECT systems were transferred to a Data General ECLIPSE-S120 or MV-7890 SH processing system and reconstructed on a 128 × 128 image matrix using Butterworth filtered backprojection. Attenuation was corrected using a pool phantom containing 110–220 MBq of ^{99m}Tc. Discrepancies in radioactivity between the right and left sides were less than 5% by region of interest (ROIs) analysis using this phantom. Linearization correction according to Lassen et al. was performed by assuming that the cerebellar blood flow without diaschisis was 55 ml/100 ml/min (*9–11*).

CT images were obtained using a General Electric 9800-HiLight system with a 10-mm slice thickness.

Study Protocol and Groups

The protocol of the present study is outlined in Figure 1. Initial CT scanning for screening preceded the SPECT examination. SPECT imaging was started 10 min after the intravenous injection of ^{99m}Tc-HMPAO (740 MBq). All SPECT images were obtained within 6 hr after the onset, and follow-up CT scanning was performed between Days 2 and 10. The plane for SPECT imaging was manually adjusted to be parallel to the orbito-meatal line in order to match the CT plane.

Using follow-up CT on morphological changes, the patients were classified into two groups: (1) an infarct group consisting of

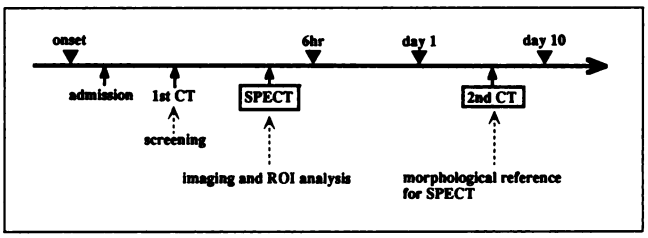

FIGURE 1. CT and SPECT protocol.

patients who showed completed infarction associated with neurological deficits and (2) a noninfarct group consisting of patients with neurological deficits on admission who showed no structural changes on follow-up CT and recovered from their deficits. The patients in the infarct group were classified on the basis of infarct area and peri-infarct area, which were respectively defined as the area of abnormal perfusion area corresponding to the low-density area on follow-up CT and the surrounding regions. SPECT lesions were visually assessed by comparison with the uptake of the contralateral normal brain and were interpreted by one to two of the authors who are experts in nuclear medicine.

ROI Selection and Data Analysis

In the infarct group, symmetrical mirror ROIs were located on the lesions and the contralateral normal brain, and the lesion-to-contralateral radioactivity ratio (L/C ratio) was calculated for both the infarct and the peri-infarct areas. The significance of the differences in the L/C ratio was determined for the infarct and peri-infarct areas. The time course of changes in the L/C ratio was assessed by comparing patients imaged within 3 hr after onset and those imaged 3–6 hr after onset. In addition, to investigate the difference of severity of ischemia in the different type of infarction, we analyzed L/C ratios of the infarct and peri-infarct area between the patients with and without cerebral embolism in this infarct group.

In the noninfarct group, no abnormal densities could be identified on follow-up CT, so mirror hemispherical ROIs were located on the right and left sides, and the right-to-left radioactivity ratio (R/L ratio) was calculated.

Statistical analysis was performed with a paired t-test.

RESULTS

Twenty-six patients were classified into the infarct group with a total of 30 infarcts on follow-up CT. The initial SPECT images showed a decrease in CBF corresponding to 27 of 30 infarct areas (Fig. 2), but the other three areas showed extremely high CBF (Fig. 3). Cerebral angiography on admission revealed early recanalization of the occluded arteries supplying two of these three hyperperfused areas, and all three areas showed typical signs of infarction on serial follow-up CT scans. Twenty of 21 patients with cerebral embolism belonged to the infarct group and all of them showed severe hypoperfusion areas consistent with completed infarction on follow-up CT.

For the peri-infarct areas, 25 showed abnormal perfusion on the initial SPECT images, and all of these areas showed mild hypoperfusion when compared to the contralateral normal brain (Fig. 2). The extent of these peri-infarct areas paralleled the distribution of the affected vascular territory of the complete infarcts. The other infarcts were associated with severe hypoperfusion of the anterior and/or middle cerebral artery territories corresponding to the actual infarct area. No peri-infarct area could be defined on the SPECT images.

Except in one case, the noninfarct group consisted of five patients who showed no perfusion abnormalities within 6 hr after the onset (Fig. 4).

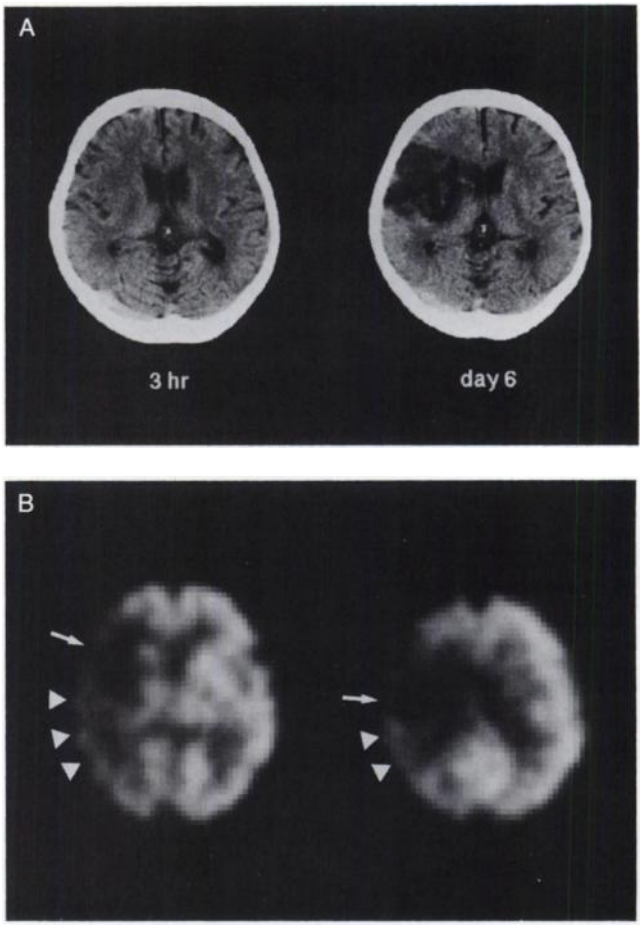

FIGURE 2. A 65-yr-old woman with sudden onset of total aphasia. (A) Axial CT image (left) obtained on admission at 3 hr after onset shows no definite abnormal density in the cerebral parenchyma. Follow-up CT image (right) obtained on Day 6 shows a completed infarct that corresponds to the area of severe hypoperfusion seen in (B). The surrounding peri-infarct area remains intact. (B) Axial SPECT images obtained at 1.8 hr after onset at approximately the same level as the images in (A) demonstrate an area of severe low perfusion (arrows) enclosed by a large area of mild hypoperfusion area (arrowheads), which is consistent with the territory of the right middle cerebral artery.

ROI Analysis

The relationship between the radioactivity ratio and the time from the onset of the ictus-to-tracer injection is illustrated in Figure 5. The earliest dot above 1.4 in the L/C ratio was observed at 1.5 hr after the onset. L/C ratios for the infarct area were used to divide the patients into hypoperfusion and hyperperfusion groups (Fig. 6). The average L/C ratio of the infarct area in the hypoperfusion group was 0.48 ± 0.14, while that of the peri-infarct area and average R/L ratio of the noninfarct group were 0.75 ± 0.10 and 0.97 ± 0.10, respectively. Thus, the L/C ratio of the infarct area was significantly lower than that of the peri-infarct area in the hypoperfusion group ($p < 0.001$), and the range of overlap between the infarct area and peri-infarct area ratios was from 0.51 to 0.67. Accordingly, completed infarction and survival of brain tissue could be distinguished

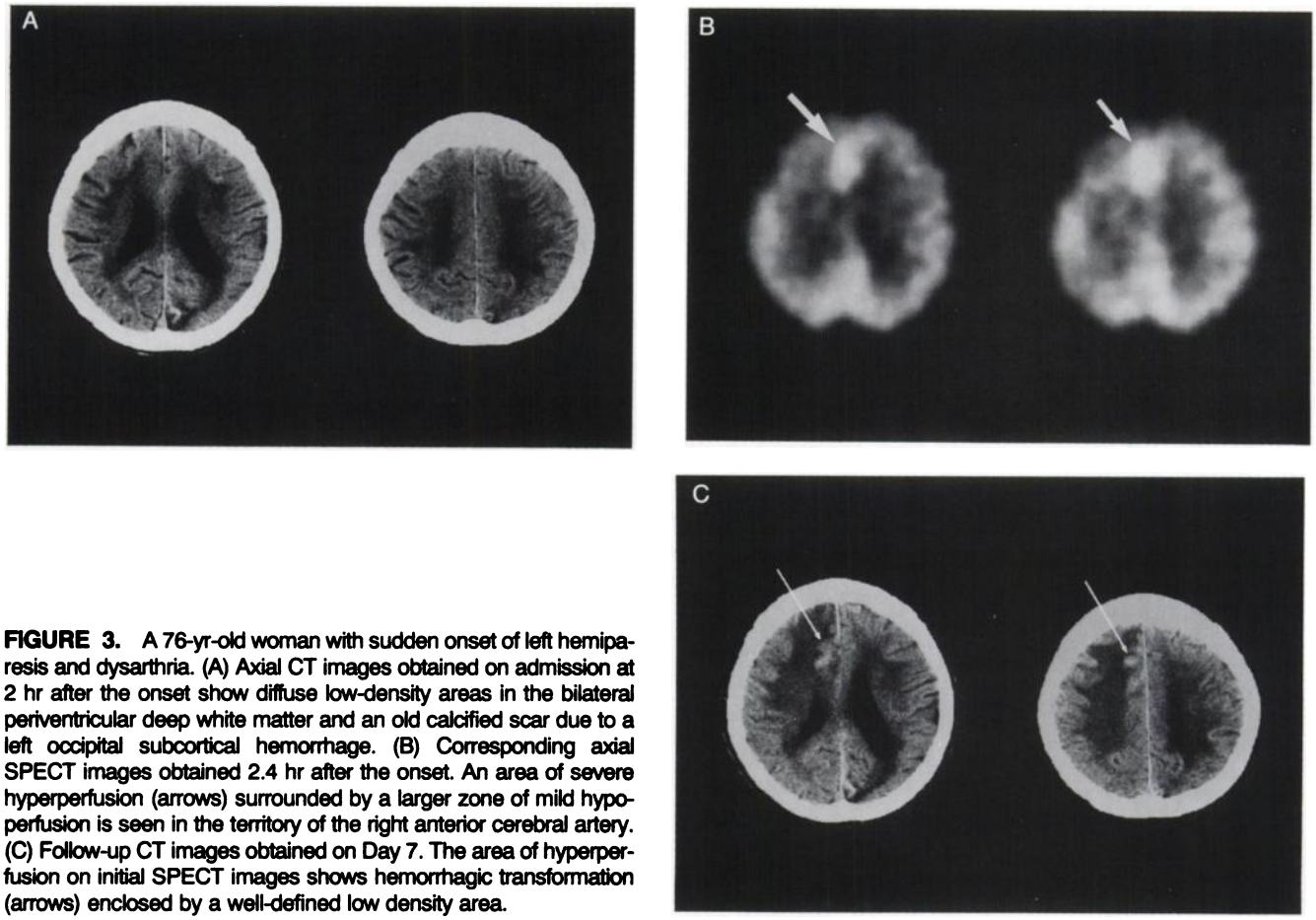

FIGURE 3. A 76-yr-old woman with sudden onset of left hemiparesis and dysarthria. (A) Axial CT images obtained on admission at 2 hr after the onset show diffuse low-density areas in the bilateral periventricular deep white matter and an old calcified scar due to a left occipital subcortical hemorrhage. (B) Corresponding axial SPECT images obtained 2.4 hr after the onset. An area of severe hyperperfusion (arrows) surrounded by a larger zone of mild hypoperfusion is seen in the territory of the right anterior cerebral artery. (C) Follow-up CT images obtained on Day 7. The area of hyperperfusion on initial SPECT images shows hemorrhagic transformation (arrows) enclosed by a well-defined low density area.

by a 40% decrease of CBF compared to the contralateral normal brain in the present SPECT analysis.

In the hypoperfusion group, a total of 22 infarct areas caused by cerebral embolism showed a remarkable decrease in L/C ratios. The average L/C ratio of these infarct areas was 0.45 ± 0.14, which was significantly lower than those of remaining five infarct areas ($p < 0.02$). The average L/C ratio of the peri-infarct areas did not show significant differences between the types of cerebral infarction.

No significant differences were observed between the average L/C ratios of the infarct and peri-infarct areas within the first 3 hr and 3–6 hr after the onset of ictus, therefore no time dependency of the L/C ratio was detected within 6 hr of infarction (Fig. 7).

DISCUSSION

Since functional imaging was introduced into the diagnosis of acute cerebral infarction, the extent of the area of ischemia considerably beyond the region of overt structural change has been pointed out by many authors (*6,12–15*). This peri-infarct hypoperfusion has been suggested to be caused by either the direct hemodynamic effects of vessel occlusion or by disconnection and deactivation of the cortex in the peri-infarct area (*6,12–15*). Selective neuronal loss is one suggested mechanism (*16–17*), though it could not be completely confirmed by a neuropathological study (*18*). The present study also demonstrated that even within 6 hr after infarction, there was an area of extremely low perfusion surrounded by a region of moderate hypoperfusion, which was consistent with the completed infarct and the surrounding normal tissue on follow-up CT scans. The area of peri-infarct hypoperfusion paralleled the vascular territory of the vessel supplying the completed infarct zone. After this short duration of ischemia, brain edema is not marked and a mass effect would not alter the blood flow in the adjacent brain tissue. The distribution of peri-infarct hypoperfusion was in accord with the result from an ^{123}I-iodoamphetamine (^{123}I-IMP) study performed in patients with subacute and chronic cerebral infarction (*15*). This indicates that it may be due mainly to direct alterations of blood flow in brain tissue with good collateral circulation, although the effect of deafferentiation cannot be completely excluded.

Focal hyperemia on SPECT images obtained within 6 hr after the ictus is a new finding in the present study. Although early angiographic vasodilatation or hyperemia (i.e., early venous filling and/or capillary blush) has already been reported in a case of temporary embolic occlusion and has been confirmed to indicate a lesion with increased CBF (*19–20*), no functional CBF studies have previously disclosed luxury perfusion within the time range that we investigated (*21–22*). In fact, a recent PET study noted

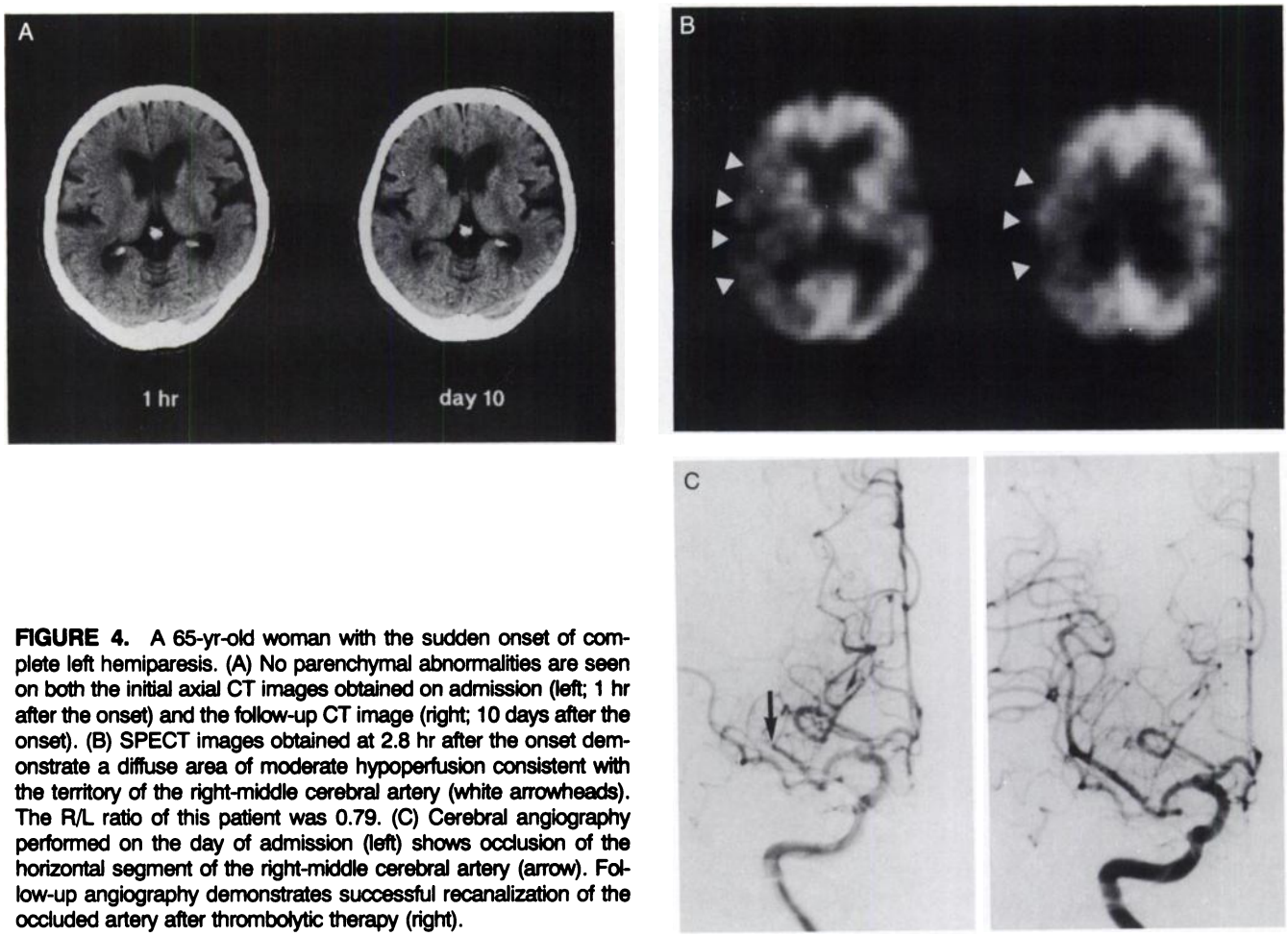

FIGURE 4. A 65-yr-old woman with the sudden onset of complete left hemiparesis. (A) No parenchymal abnormalities are seen on both the initial axial CT images obtained on admission (left; 1 hr after the onset) and the follow-up CT image (right; 10 days after the onset). (B) SPECT images obtained at 2.8 hr after the onset demonstrate a diffuse area of moderate hypoperfusion consistent with the territory of the right-middle cerebral artery (white arrowheads). The R/L ratio of this patient was 0.79. (C) Cerebral angiography performed on the day of admission (left) shows occlusion of the horizontal segment of the right-middle cerebral artery (arrow). Follow-up angiography demonstrates successful recanalization of the occluded artery after thrombolytic therapy (right).

hyperperfusion with little metabolic alteration at 5–18 hr after the onset of cerebral infarction (*23*). In the present SPECT study, hyperemic lesions were observed from 1.5 hr after the ictus. Two of the three patients with these lesions underwent cerebral angiography on the day of admission and one had multiple occluded vessels with fragmentation of emboli in the corresponding distribution. The other patient showed only a slight angiographic blush that was consistent with the completed infarct area. These findings strongly suggest early recanalization of an occluded artery and may represent the phenomenon of "postischemic hyperemia" (*13*). Angiographic recanalization has been reported within 24 hr after cerebral infarction (*24*) and is supposed to accelerate the increase of local CBF caused by vasodilatation in response to a decreased tissue pH along with the elevation of lactic acid. An experimental study has demonstrated that the magnitude and duration of reactive hyperemia are related to the magnitude and duration of CBF reduction (*3*). Although reperfusion is generally regarded as an indicator of a good clinical outcome (*23*), marked early focal hyperemia may follow critical ischemia and thus may indicate irreversible brain damage. The fact that all of the hyperemic regions in the present study corresponded to low-density areas on follow-up CT scans would support this suggestion.

Development of cerebral infarction is related to the severity and duration of ischemia, so a simple method of flow threshold determination is needed when therapeutic intervention is under consideration. Although the possibility of luxury perfusion cannot be excluded even when rCBF is within a normal range and CBF measurement alone cannot differentiate metabolic inactivity from normal tissue function (*25*), we tried to set an ischemic threshold of morphological change for SPECT measurement of CBF by comparing the L/C ratios between infarct and peri-infarct areas. The group with hypoperfusion of the infarct area showed a 52% decrease in CBF when compared to the contralateral normal brain. Considering the lowest L/C ratio of the peri-infarct area, a decrease of approximately 40% in CBF compared to the contralateral normal brain appears to represent the borderline between reversible and irreversible structural brain damage in the present series. However, an L/C ratio above 0.6 in the infarct area may also include relatively hyperemic lesions with reduced metabolism, so measurement of cerebral metabolism may be necessary for the accurate determination of an ischemic threshold. Therefore, our findings would suggest that a patient with an L/C ratio considerably below 0.6 should not be included in a trial of therapeutic reperfusion, even if seen within 6 hr of the ictus.

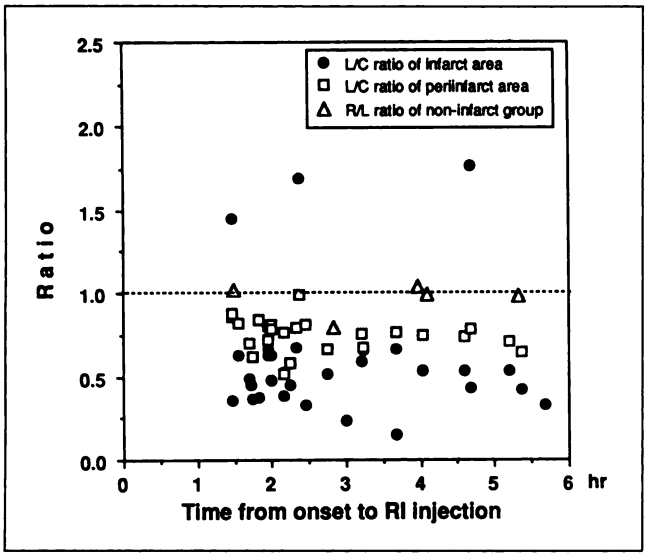

FIGURE 5. A scatter plot of the L/C and R/L SPECT ratios versus the time of radiotracer injection after onset. The earliest L/C ratio above 1.4 was observed at 1.5 hr from onset.

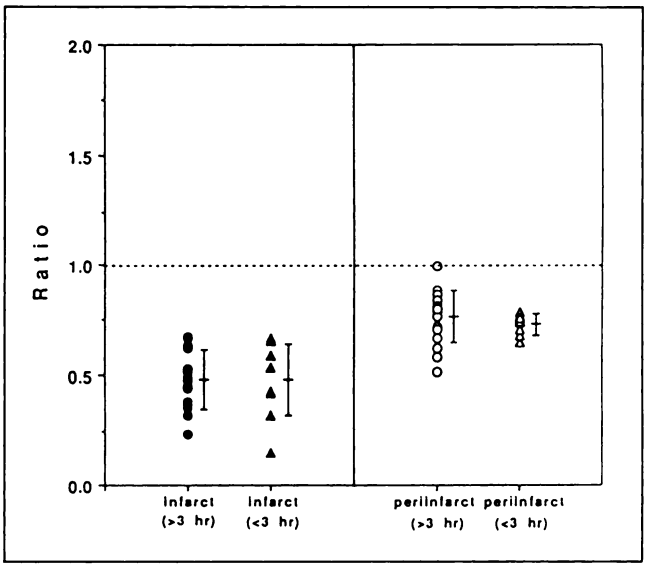

FIGURE 7. Comparison of the average L/C ratios of the infarct and peri-infarct areas in relation to the duration of ischemia. There is no time dependency of the L/C ratio within this time range.

Types of strokes have been known to affect the clinical course of the patient; the selection of therapy would be different among the causes of ischemia. Cerebral embolism is one of the most applicable targets of early interventional treatment, however, few hemodynamic studies have been investigated in acute stages of infarction. The present study demonstrates that CBF of the infarct area was remarkably reduced just after onset of ischemia when the cause was induced by cardiogenic emboli. Remediable time range would be short in this kind of infarction so that rapid estimation of CBF by SPECT may offer information in the choice of therapy and prediction of the clinical course.

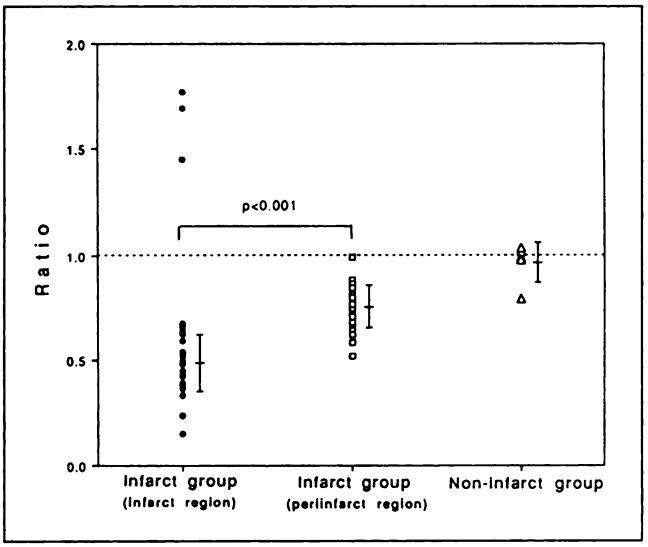

FIGURE 6. L/C SPECT ratios of the infarct and peri-infarct areas in the infarct group and the R/L SPECT ratios of the noninfarct group. The average L/C ratio of the infarct area in the hypoperfusion group was significantly lower than that of the peri-infarct area ($p < 0.001$).

Quantitative CBF measurement has given a lower ischemic threshold than that obtained in the present SPECT study (*5,15*). Various methodological differences may be related to this discrepancy. For example, scattered radiation has more effect on SPECT imaging than on PET imaging. Without scatter correction, the CBF values for both the ischemic region and the normal brain are overestimated by SPECT, and the magnitude of the error would be greater in the better perfused areas. Lower spatial resolution could be another reason for the higher SPECT threshold because of the lack of separation of CBF in the gray and white matter or in the infarct and peri-infarct areas. In addition, when the cerebellar CBF used for the reference is lower than 55 ml/100 ml/min, underestimation of the contralateral normal CBF may occur after linearization correction (*26*), and this would make the denominator of the L/C ratio smaller compared to that obtained in PET studies. The pharmacokinetics of ^{99m}Tc-HMPAO provide another reason for the overestimation of CBF in the infarct and peri-infarct areas. SPECT can exaggerate the CBF in these areas by including the plasma activity in the dilated vascular component (*27–28*). In the present study, the area of hyperperfusion in the infarct group may have been overestimated because it contained an increased cerebral blood volume. Comparative SPECT studies using ^{123}I-IMP and ^{133}Xe have shown that the infarct and asymptomatic thresholds of the L/N ratio obtained by ^{123}I-IMP SPECT are 39–48% and 65–72%, respectively (*5,29*). Both of these thresholds are lower than that obtained in our study. They correlated well with the data obtained by PET or ^{133}Xe SPECT. Differences in the kinetic behavior of the tracers may have contributed to this discrepancy as well as to the methodological differences in CBF measurement.

The population in the present study consisted of patients with a mixture of temporary and permanent vascular oc-

clusion. Thus, it should be taken into account that the previous data on ischemic threshold, both of morphological and symptomatic changes, were mostly determined by the clinical studies performed more than 6 hr after the onset of symptoms or by investigating an animal model (*3,4,12,14,23,25,29*). The different examination times for PET and SPECT studies of CBF may be one of the reasons for the different thresholds. A recent PET study using an animal model of permanent middle cerebral artery occlusion revealed that the CBF in the affected cortex immediately after occlusion ranged from ~50% to 67% of that in the contralateral cortex (*30*). These values were higher than those obtained in PET studies of chronic cerebral infarction and were compatible with the results of the present study. The heterogeneity of the ischemic state in our clinical population would be an additional factor in the higher L/C ratios of both groups and the lack of a time-dependent decrease.

CONCLUSION

The present study detected hyperemia and the critical blood flow level in a very early stage of cerebral ischemia. Although SPECT measurement has some drawbacks in estimating quantitative CBF, it provides information for evaluating hemodynamic alterations in patients with acute cerebral ischemia and should help to determine whether interventional reperfusion is worthwhile. Further investigation to allow more precise evaluation of blood flow and metabolic parameters within this time range may be worthwhile when noninvasive systems for quantitative measurement of brain function have been developed that can be applied in the emergency setting.

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