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*AJNR Am J Neuroradiol* 1996, 17 (9) 1661-1668

<http://www.ajnr.org/content/17/9/1661>

This information is current as  
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# Complete Recanalization via Fibrinolytic Therapy Can Reduce the Number of Ischemic Territories That Progress to Infarction

Osamu Sasaki, Shigekazu Takeuchi, Takayuki Koizumi, Tetsuo Koike, and Ryiichi Tanaka

**PURPOSE:** To clarify the clinical significance of fibrinolytic therapy for acute ischemic stroke.

**METHODS:** We analyzed findings in 18 patients with occlusion of a major artery in respect to cerebral blood flow thresholds for infarction. Nine of these patients had shown complete recanalization just after the treatment, between 3.5 and 7.25 hours after symptom onset, and the other nine had shown no change. Cerebral blood flow was measured by single-photon emission CT using  $^{99m}\text{Tc}$ -labeled hemamethylpropyleneamine oxime and assessed semiquantitatively: multiple regions of interest were placed on the section images and two parameters, the R/CL ratio and the R/CE ratio, were calculated (where R represents a mean count of the region of interest in the affected hemisphere, CL on the opposite side, and CE in the cerebellar hemisphere on the affected ischemic side). **RESULTS:** Reperfusion significantly reduced the development of infarction in the regions of interest with an R/CL ratio between 0.65 and 0.85 or an R/CE ratio between 0.55 and 0.75. No correlation was observed between the development of infarction and the duration of ischemia. The cerebral blood flow threshold in patients without recanalization was higher than that in patients with recanalization. **CONCLUSION:** Reperfusion achieved by fibrinolytic therapy in the acute stage can save ischemic brain within a limited cerebral blood flow value.

**Index terms:** Brain, infarction; Brain, ischemia; Cerebral blood flow; Therapeutic radiology

*AJNR Am J Neuroradiol* 17:1661–1668, October 1996

In the treatment of acute ischemic stroke, restoration of blood flow is essential to protect ischemic brain from infarction, and fibrinolytic therapy has been a useful strategy to recanalize an occluded artery. Although the rate of recanalization with this therapy was low until recently, it has been raised by intraarterial or local intraarterial infusion of fibrinolytic agents as well as by the advent of fibrin-selective agents without any excess risk of hemorrhagic infarction (1–7). However, the efficacy of this therapy has yet to be refined, because recanalization does not always bring about clinical improvement or reduction in infarct size (3, 5, 8).

It is well known that recovery of ischemic brain or development of infarction is largely dependent on the intensity and the duration of ischemia (9–12). The former is related to residual blood flow and the latter to the timing of the treatment. Therefore, estimation of the residual flow is important to predict the effect of reperfusion achieved by the therapy. However, there are scarce data on the critical flow and period of ischemia that can be tolerated in humans (10, 13).

In a previous report we analyzed results of a large group of patients with acute embolic stroke treated with local intraarterial infusion as compared with groups treated with intravenous or intracarotid infusion of high-dose fibrinolytic agents. The results suggested that local infusion brings about a high rate of recanalization, clinical improvement, and a reduction in infarction size in selected patients (3). In the present study, we explored cerebral blood flow (CBF) thresholds for infarction using computed tomography (CT) and single-photon emission CT

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Received August 16, 1995; accepted after revision March 5, 1996.

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*AJNR* 17:1661–1668, Oct 1996 0195-6108/96/1709–1661

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(SPECT) in patients who showed either complete or no recanalization after fibrinolytic therapy. Our purpose was to assess the effect of reperfusion on patients with acute ischemic stroke as a function of CBF.

## Subjects and Methods

Since 1989, most of our patients with acute ischemic stroke have been treated with fibrinolytic therapy, and more than 60 patients received local intraarterial infusion of high-dose fibrinolytic agents at our hospital. Recently, we also started intravenous administration of alteplase (recombinant tissue plasminogen, rt-PA). Inclusion criteria for fibrinolytic therapy in the present study were occlusion of a major artery as demonstrated by angiography within 6 hours after the onset of symptoms, no fresh infarct on CT scans at admission, and informed consent from patients or from a member of their family. The local infusion was performed with a Tracker microcatheter (Target Therapeutics, Los Angeles, Calif), and 10 mega-international units (MIU) (approximately 20 mg) of alteplase or  $24 \times 10^4$  to  $36 \times 10^4$  IU of urokinase. The drug was dissolved in 40 mL normal saline and injected through a catheter that was positioned into or as close as possible to an embolus for 20 minutes (3). If complete recanalization was not achieved, a second or a third infusion was performed. Follow-up angiography was done the next day using a sheath catheter in the femoral artery sutured in place. The intravenous treatment was performed with 20 MIU of alteplase for 60 minutes.

From these patients we selected 18 who were studied with SPECT before fibrinolytic therapy and who showed either complete or no recanalization just after the therapy. The patients showing partial recanalization were excluded from the study, because their restoration of blood flow was not sufficient to allow us study precise relationships between critical blood flow and the period of ischemia.

Each patient received a small dose of heparin (<5000 units) just before angiography that was discontinued after the infusion was completed. No special treatment, such as hemodilution therapy, was given, and administration of warfarin or aspirin was delayed for at least 1 or 2 weeks.

In evaluating recanalization, the following three grades were used: complete recanalization, in which clot lysis was complete and blood flow was fully restored on angiography done just after the infusion of a drug; partial recanalization, in which restoration of blood flow was insufficient owing to partial clot lysis; and no recanalization.

The Glasgow Outcome Scale was used to evaluate the clinical outcome at 3 months after symptom onset. To assess the occurrence of hemorrhagic infarction, we obtained CT scans immediately after and within 24 hours after completion of the therapy. Follow-up CT scans were obtained 3 days, 1 week, 2 weeks, and more than 1 month later. Statistical analysis was done using a  $\chi^2$  test and the results were expressed by *P* values; *P* values less than .05 were considered statistically significant.

## SPECT Studies

SPECT with  $^{99m}\text{Tc}$ -labeled hemamethylpropyleneamine oxime (HMPAO) was performed using a high-resolution multiple-section SPECT Headtome Set-050 (Shimazu, Tokyo, Japan). This system has a circular detector array consisting of 96 NaI bar crystals and 96 photomultiplier tubes and can make 20 images simultaneously. SPECT images were obtained 5 minutes after intravenous injection of  $^{99m}\text{Tc}$ -HMPAO (20 to 30 mCi, Ceretec; Amersham, Japan) with a sampling matrix of  $64 \times 64$ . Transverse tomographic images with a thickness of 10 mm were reconstructed at 5-mm intervals, resulting in 19 axial sections. Linearization correction, in accordance with Lassen et al (14), was not performed, because corrected images could not be obtained using our SPECT system. SPECT scans usually took about 25 to 30 minutes.

Three of the 19 axial sections were selected for study: one included the cerebellar hemisphere, another the anterior horn of the lateral ventricle, and the third the body of the lateral ventricle. We selected  $12.5 \times 12.5$ -mm square regions of interest on the three sections. Multiple regions of interest were placed symmetrically in the frontal, temporal, parietal, and occipital cortices, the basal ganglia, the white matter of each hemisphere, and the cerebellar hemispheres (Fig 1). When CT scans demonstrated an old low-density area in the hemisphere, regions of interest were not placed in this area. To assess CBF semiquantitatively, two parameters were calculated: the ratio of ischemic regional activity (R) to contralateral regional activity (CL) ( $R/CL$  ratio =  $A/B$ ) and the ratio of R to cerebellar activity (CE) ( $R/CE$  ratio =  $A/C$ ), where A represents a mean count of the regions of interest in the affected hemisphere, B that on the opposite side, and C that in the cerebellar hemisphere on the affected side. Location of the regions of interest was judged to be in the normal area, in the infarct area, or in the margin that included both the infarct and normal areas, by manually superimposing the SPECT scans on the CT scans obtained during the chronic stage.

## Results

### Patients' Characteristics

Patients' characteristics are presented in Table 1. Nine patients showed no change and the other nine showed complete recanalization just after the therapy. Of the nine patients showing no change, seven were treated with local intraarterial infusion of the drug and two were treated with intravenous infusion. In three patients the internal carotid artery was involved and in six the middle cerebral artery was involved. Of the nine patients with complete recanalization, eight were treated with local infusion (seven with urokinase and one with

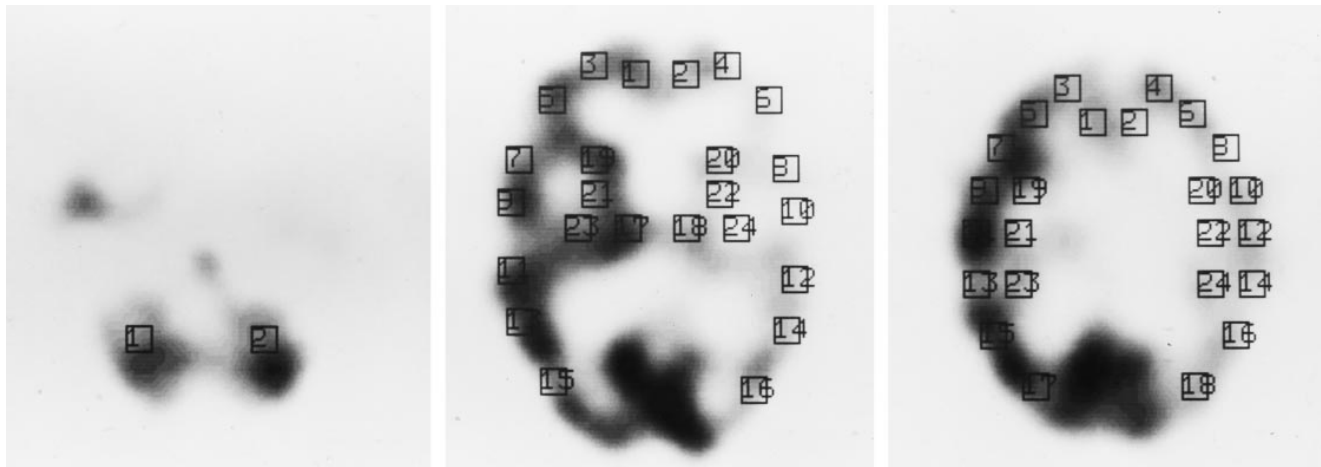


Fig 1. SPECT scans show placement of regions of interest.

alteplase). The middle cerebral artery was involved in seven, and the origin was embolic in seven. The size of the infarctions with complete recanalization was smaller and the outcome of the patients was better than in patients who showed no change. Hemorrhagic infarction was seen in four of nine patients in both groups. Only one patient in the recanalized group deteriorated clinically, having developed a large hematoma in the basal ganglia just after the treatment.

### *CBF Threshold for Infarction*

Correlations between the residual CBF as defined by two indexes and the development of infarction in the recanalized and nonrecanalized groups are presented in Table 2 and Figures 2 and 3. The average R/CL ratios in normal, marginal, and infarct regions in the recanalized group were  $0.87 \pm 0.11$ ,  $0.74 \pm 0.13$ , and  $0.52 \pm 0.24$ , respectively, whereas those in the nonrecanalized group were  $0.85 \pm 0.11$ ,  $0.74 \pm 0.08$ , and  $0.54 \pm 0.19$ , respectively. As a whole, no differences were observed in the average R/CL ratios between the two groups. There was no significant difference in the development of infarction between the two groups for the regions with an R/CL ratio less than 0.65 or an R/CE ratio less than 0.55 as well as in the regions with an R/CL ratio greater than 0.85 or an R/CE ratio greater than 0.75. Occurrence of infarction was significantly reduced in the recanalized group when the regions revealed an R/CL ratio of 0.65 to 0.85 or an R/CE ratio of 0.55 to 0.75.

The relationship between CBF threshold for infarction and duration of ischemia is shown in Figures 4 and 5. There was no correlation when recanalization was performed between 3.5 and 7.25 hours after symptom onset (Fig 4). However, in the recanalized group, a clear distinction was shown between the regions that progress to infarction and other regions around the R/CL ratio of 0.65 (Figs 2 and 4). There were some uncommon regions of interest of infarction when the R/CL ratio was more than 1.1.

The CBF threshold for infarction in the nonrecanalized group is shown in Figure 5. The boundary between the regions leading to infarction and other territories was overlapping and obviously located in a higher place. The R/CL ratio was between 0.65 and 0.8.

## **Discussion**

### *Fibrinolytic Therapy*

The rationale for fibrinolytic therapy for acute ischemic stroke is dependent on two steps: recanalization of an occluded artery and recanalization followed by clinical improvement (2). Therefore, to elucidate the efficacy of this therapy, at least two issues must be addressed: one is whether a sufficient rate of recanalization can be achieved by the therapy and the other is whether the recanalization is beneficial in improving outcome or in preventing cerebral infarction. A number of researchers have investigated this therapy from the viewpoints of drugs, dose, and route of administration, and reports have indicated an increase in the use of intraar-

TABLE 1: Eighteen patients with acute ischemic stroke treated with fibrinolytic therapy

Case	Age, y/ Sex	Origin	Site of Occlusion	Treatment			Interval, h	Recanalization	Clinical Improvement	Size of Infarct	Hemorrhagic Change?	Clinical Outcome (GOS)	Second Angiography	
				Administration	Drug	Dose							Interval, h	Recanalization
1	75/M	Embolic	M1	IV	Alteplase	$20 \times 10^6$	2.5	...	...	Large	Yes	SD	23	...
2	78/F	Embolic	M1	IV	Alteplase	$20 \times 10^6$	4.5	...	...	Large	No	Died	27	...
3	78/M	Embolic	M2	Local	Urokinase	$72 \times 10^4$	3	...	...	Small	No	SD	22	...
4	75/M	Embolic	M1	Local	Urokinase	$96 \times 10^4$	3	...	...	Large	Yes	Died	20	Complete
5	75/M	Embolic	ICA	Local	Urokinase	$42 \times 10^4$	4	...	...	Large	No	Died	27	...
6	53/M	Embolic	M1	Local	Urokinase	$60 \times 10^4$	4.5	...	...	Large	Yes	SD	24	Partial
7	77/F	Embolic	ICA	Local	Urokinase	$42 \times 10^4$	5	...	...	Large	No	PVS	22	...
8	70/F	Embolic	ICA	Local	Urokinase	$96 \times 10^4$	6	...	...	Large	Yes	Died	...	...
9	72/M	Embolic	M2	Local	Urokinase	$84 \times 10^4$	7	...	...	Medium	No	GR	34	Complete
10	60/F	Embolic	M2	Local	Urokinase	$54 \times 10^4$	3.5	Complete	Improved	...	No	GR	...	...
11	68/F	Embolic	M2 and A1	Local	Urokinase	$84 \times 10^4$	4	Complete	Improved	Medium	No	MD	...	...
12	74/F	Embolic	M1	Local	Urokinase	$54 \times 10^4$	4.5	Complete	Worsened	...	Hematoma SD	...	...	...
13	61/M	Embolic	M1	Local	Urokinase	$96 \times 10^4$	5.25	Complete	...	Large	Yes	SD	...	...
14	62/M	Embolic	M2	Local	Urokinase	$54 \times 10^4$	5.8	Complete	...	Small	Yes	GR	13	Complete
15	70/F	Embolic	M1	Local	Alteplase	$20 \times 10^6$	7	Complete	Improved	Small	No	GR	20	Complete
16	80/F	Embolic	M2	IV	Alteplase	$20 \times 10^6$	7.25	Complete	...	Large	Yes	MD	...	...
17	65/M	Thrombotic	M1	Local	Urokinase	$96 \times 10^4$	5.5	Complete	Improved	Large	No	Died	14	Complete
18	71/M	Thrombotic	M1	Local	Urokinase	$42 \times 10^4$	5.3	Complete	Improved	...	No	GR	24	Complete

Note.—M1 indicates M1 portion of the middle cerebral artery; M2, M2 portion of middle cerebral artery; ICA, internal carotid artery; A1, A1 portion of anterior cerebral artery; IV, intravenous; local, local intraarterial; interval, time from onset of symptoms to recanalization; GOS, Glasgow Outcome Scale; SD, severe disability; PVS, persistent vegetative state; GR, good recovery; and MD, moderate disability.

TABLE 2: R/CL ratio\* in recanalized and nonrecanalized groups

	Regions of Interest, n	R/CL Ratio (mean $\pm$ SD)
Recanalized		
Normal	160	0.87 $\pm$ 0.11
Marginal	10	0.74 $\pm$ 0.13
Infarct	46	0.52 $\pm$ 0.24
Nonrecanalized		
Normal	61	0.85 $\pm$ 0.11
Marginal	28	0.74 $\pm$ 0.08
Infarct	87	0.54 $\pm$ 0.19

\* R/CL ratio indicates the ratio of ischemic regional activity to contralateral regional activity.

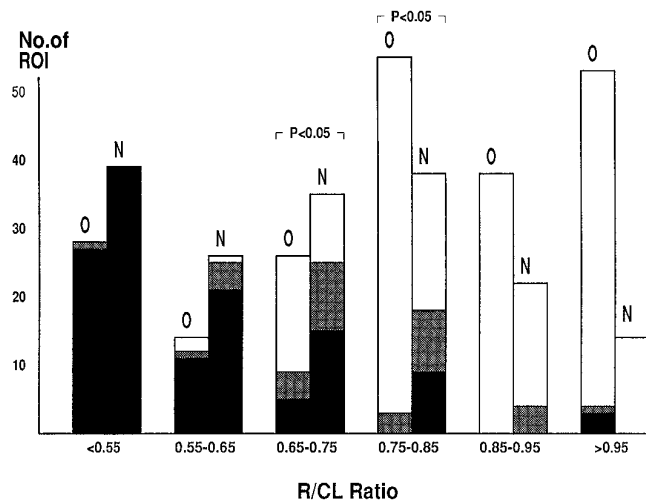


Fig 2. Relation between development of infarction and ratio of ischemic regional activity to contralateral regional activity (R/CL ratio = A/B), where A represents a mean count of the region of interest on the ischemic side and B represents that on the opposite side. O indicates open; N, not open; white areas, normal; stippled areas, margin; and black areas, infarct.

terial or local infusion of drugs in relation to recanalization therapy (1–7). However, the clinical efficacy of fibrinolytic therapy for acute ischemic stroke remains undetermined, because the clinical significance of recanalization is still controversial: some investigators have reported that reperfusion in the acute stage is related to a good outcome (1–7) while others have suggested that restoration of blood flow is not associated with smaller brain infarcts or does not improve clinical outcome (3, 5, 15). In this study we measured CBF and explored CBF thresholds for cerebral infarction in order to clarify the effect of recanalization more objectively.

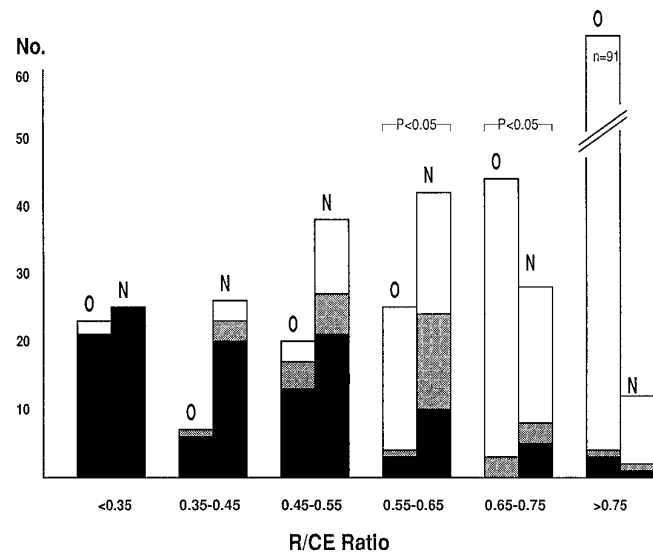


Fig 3. Relation between development of infarction and ratio of ischemic regional activity to cerebellar activity (R/CE ratio = A/C), where C represents a mean count of the region of interest in the cerebellar hemisphere on the ischemic side. O indicates open; N, not open; white areas, normal; stippled areas, margin; and black areas, infarct.

### CBF Threshold for Infarction

The reversibility of ischemic brain has been well investigated in animal experiments; results suggest that the degree and duration of ischemia is strongly related to the development of neuronal damage (9–12). The value of CBF for reversible brain damage appears to be between 10 to 20 mL/100 g per minute (9, 10, 16), although it might be lower when the interval of occlusion is shorter. However, little comparable data are available for human subjects. In a few studies using stable xenon-enhanced CT or positron emission tomography (PET), the value of 10 to 22 mL/100 g per minute has been reported to be critical (8, 17–20). However, these studies consisted of patients in whom re-establishment of blood flow was unclear or not done. Therefore, the results do not show the precise CBF threshold for infarction or the correlation between the flow threshold and the critical period of ischemia. In this study, the number of patients was small, but they were restricted to those in whom angiograms obtained just after treatment to evaluate the exact time of ischemia showed either complete recanalization or no recanalization.

CBF was measured by using  $^{99m}\text{Tc}$ -HMPAO SPECT studies. This technique does not offer a

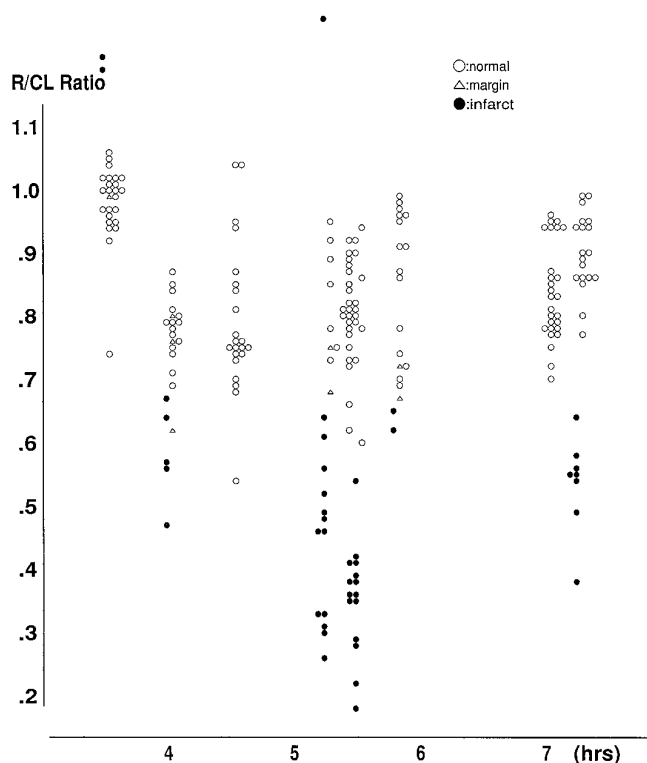


Fig 4. CBF R/CL ratio versus time to recanalization in patients with successful recanalization.

quantitative measurement of blood flow, but it facilitates emergency CBF studies and makes the rapid semiquantitative evaluation possible. The usefulness of this technique for examining patients with acute ischemic stroke has been reported in the literature (4, 21, 22). In this study, an R/CL ratio and an R/CE ratio were used as parameters, and our results showed that in the regions with an R/CL ratio between 0.65 and 0.85 or an R/CE ratio between 0.55 and 0.75, reperfusion significantly reduced the occurrence of cerebral infarction. The threshold of the R/CL ratio for infarction in the recanalized group was 0.65 and that in the nonrecanalized group was obviously higher.

Infarction occurs with severe ischemia regardless of recanalization, and it does not develop with mild ischemia even without recanalization. In a comparative SPECT study, the R/CL ratios of reversible ischemic regions were shown to be  $0.55 \pm 0.05$  by *N*-isopropyl-p-[ $^{123}\text{I}$ ] iodoamphetamine ( $^{123}\text{I}$  IMP) and  $0.64 \pm 0.04$  by HMPAO (21). In another study of cerebral infarction within 6 hours of onset, the R/CL ratios for the infarct and periinfarct regions were  $0.48 \pm 0.14$  and  $0.75 \pm 0.10$  by HMPAO (22). These values are similar to ours. However, our values

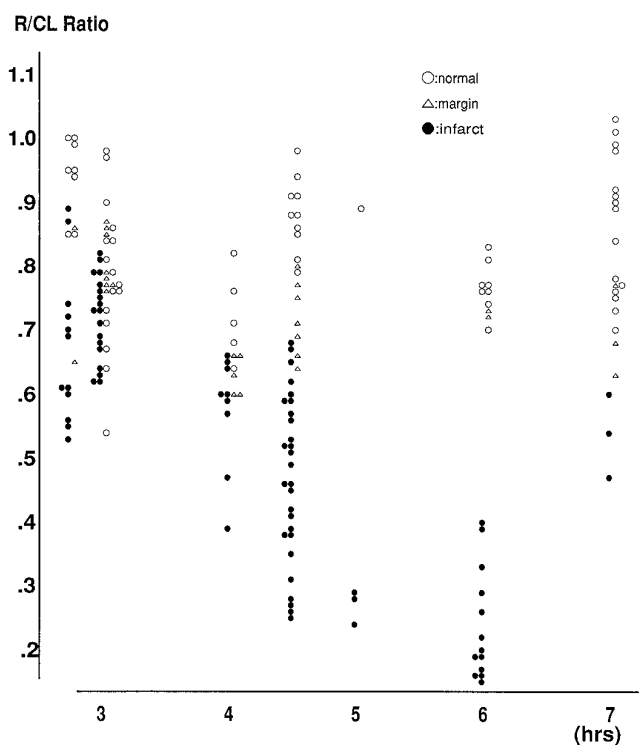


Fig 5. CBF R/CL ratio versus time from symptom onset to angiography in patients who did not have recanalization.

might have been lower if linearization correction, which was done in those two studies in accordance with Lassen et al (14), had been done in ours. The CBF infarction thresholds suggested by the HMPAO SPECT studies are slightly higher than those obtained in animal experiments or in human studies done with PET, xenon-enhanced CT, or  $^{123}\text{I}$ -IMP SPECT (21, 22). This difference might be due to the methods used to measure CBF or to the specific pharmacokinetic character of the  $^{99\text{m}}\text{Tc}$ -HMPAO. The present study also suggests that R/CL values above the usual threshold do not always indicate viable tissue. Infarction occurred in some regions of interest with a higher value, perhaps because the measurements were made during the period of luxury perfusion.

#### Critical Period of Ischemia

For patients with ischemic stroke, it is important to know the critical period of ischemia in order to determine whether to initiate recanalization therapy. In animal experiments, a period

of 2 to 8 hours of ischemia has been determined as critical, depending on the species (9, 11, 12, 15, 23). In humans, 2 to 3 hours of ischemia usually causes no or only focal infarction (9, 11, 23), whereas a period of 6 hours of severe ischemia is generally considered to be critical (6, 7, 24). Zeumer et al (7) have estimated that thrombolytic therapy for occlusion of the internal carotid artery or middle cerebral artery should be started no later than 5 hours after the onset of stroke. Yamaguchi et al (6) suggest that the therapeutic window is approximately 6 hours after onset, whereas others consider 6 hours of occlusion too long (3, 15). The present study has not clearly defined a critical period of occlusion but it has demonstrated that reperfusion achieved between 3.5 and 7.25 hours after symptom onset is beneficial and that the occurrence of infarction after recanalization is not only related to the duration of ischemia but also to the degree of ischemia. These results agree with those by Weinstein et al (12), who reported that both neurologic and pathologic responses to 5-, 6-, and 8-hour temporary occlusion were similar. Predicting the development of infarction solely on the basis of the duration of ischemia might be difficult because of the variability of CBF during occlusion (3, 11, 24). We have no data as to whether the threshold becomes lower when blood flow is reestablished within 3 hours after symptom onset. However, performing recanalization within a few hours does not appear to be practical. The significance of reperfusion 8 hours after symptom onset is also unknown. Further studies are required to clarify the relation between the CBF threshold and the critical period of ischemia.

Hemorrhagic infarction has been considered to be a serious risk associated with thrombolytic therapy. However, recent studies have indicated that the rate of hemorrhagic infarction after fibrinolytic therapy is not high when compared with that which occurs naturally (1–6, 12). Recently, Ueda et al (4) have reported that hemorrhagic transformation after fibrinolytic therapy occurs in patients with an R/CE ratio of less than 0.35. This value is far below the threshold for infarction, and fibrinolytic therapy is not recommended according to our data.

In conclusion, the present study has provided evidence that reperfusion achieved by fibrinolytic therapy initiated between 3.5 and 7.25 hours after symptom onset reduces the chances of cerebral infarction developing in regions with

CBF values defined as an R/CL ratio between 0.65 and 0.85 or an R/CE ratio between 0.55 and 0.75 by HMPAO SPECT. Although this measurement is semiquantitative in nature, pretherapeutic evaluation of CBF appears to be useful for selecting patients who are likely to benefit clinically from fibrinolytic therapy.

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